6,7-DIHYDRO-5*H*-PYRAZOLO[1,2-*a*]PYRAZOL-1-ONES WHICH PROVIDE ANALGESIA

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CROSS REFERENCE TO RELATED APPLICATIONS

This application in a Continuation-In-Part Application of Application Serial No. 10/246,214 filed September 18, 2002, which claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/323,625, filed September 20, 2001.

FIELD OF THE INVENTION

The present invention relates to 6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-ones which are capable of providing pain relief to humans and higher mammals. The present invention encompasses pharmaceutical compositions and methods for controlling pain and providing analgesia to humans and higher mammals. The present invention further relates to methods and compositions for use as therapies in other diseases affected by cytokine activity.

BACKGROUND OF THE INVENTION

Interleukin –1 (IL-1) and Tumor Necrosis Factor-α (TNF-α) are among the important biological substances known collectively as "cytokines." These molecules are understood to mediate the inflammatory response associated with the immunological recognition of infectious agents.

These pro-inflammatory cytokines are suggested as an important mediators in many disease states or syndromes, *inter alia*, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease (IBS), septic shock, psoriasis, cardiopulmonary dysfunction, acute respiratory disease, cachexia, and therefore responsible for the progression and manifestation of human disease states.

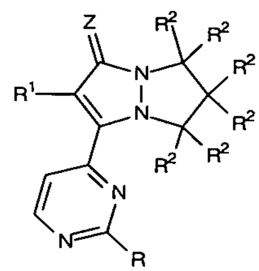
There is also a long felt need for compounds, pharmaceutical compositions, and methods for providing relief of chronic or acute pain.

SUMMARY OF THE INVENTION

It had further been surprisingly discovered that the compounds disclosed herein are effective in providing analgesia and other forms of pain relief to humans and higher mammals.

The first aspect of the present invention relates to methods for reducing pain and thereby providing analgesia to humans and higher mammals, said method comprising the step of

administering to a human or high mammal an effective amount of a compound, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_kR^3$; or

b) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl or alkylenearyl, substituted or unsubstituted heteroaryl or alkyleneheteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_mR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index m is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

each R^2 unit is independently selected from the group consisting of:

a) hydrogen;

b) $-(CH_2)_jO(CH_2)_nR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) $-(CH_2)_jOCON(R^{10})_2$;

h) two R^2 units can be taken together to form a carbonyl unit;

i) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5, n is an index from 0 to 5;
Z is O, S, NR^{11}, or NOR^{11}; R^{11} is hydrogen or C_1-C_4 alkyl.

The second aspect of the present invention relates to methods for reducing inflammatory bowel disease (IBS) in humans and higher mammals, said method comprising the step of administering to a human or high mammal an effective amount of a 6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-one according to the present invention.

The third aspect of the present invention relates to methods for reducing psoriasis in humans and higher mammals, said method comprising the step of administering to a human or high mammal an effective amount of a 6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-one according to the present invention.

The fourth aspect of the present invention relates to methods for controlling disease states selected from the group consisting of congestive heart failure, hypertension, chronic obstructive pulmonary disease, septic shock syndrome, tuberculosis, adult respiratory distress asthma, atherosclerosis, muscle degeneration, periodontal disease, cachexia, Reiter's syndrome, gout, acute synovitis, eating disorders including anorexia, bulimia nervosa, fever, malaise, myalgia and headaches.

These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{O} C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for providing pain relief to humans and higher mammals. This is accomplished by administering to a human or higher mammal a compound as further described herein below, or alternatively an admixture of two or more of said compounds.

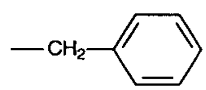
The present invention further relates to pharmaceutical compositions which comprise an effective amount of one or more analgesia producing compounds in addition to one or more "common" pain relief ingredients.

For the purposes of the present invention the term "hydrocarbyl" is defined herein as any organic unit or moiety which is comprised of carbon atoms and hydrogen atoms. Included within the term hydrocarbyl are the heterocycles which are described herein below. Examples of various unsubstituted non-heterocyclic hydrocarbyl units include pentyl, 3-ethyloctanyl, 1,3-dimethylphenyl, cyclohexyl, cis-3-hexyl, 7,7-dimethylbicyclo[2.2.1]-heptan-1-yl, and naphth-2-yl.

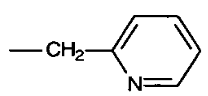
Included within the definition of "hydrocarbyl" are the aromatic (aryl) and non-aromatic carbocyclic rings, non-limiting examples of which include cyclopropyl, cyclobutanyl, cyclopentanyl, cyclohexane, cyclohexenyl, cycloheptanyl, bicyclo-[0.1.1]-butanyl, bicyclo-[0.1.2]-pentanyl, bicyclo-[0.1.3]-hexanyl (thujanyl), bicyclo-[0.2.2]-hexanyl, bicyclo-[0.1.4]-heptanyl (caranyl), bicyclo-[2.2.1]-heptanyl (norboranyl), bicyclo-[0.2.4]-octanyl (caryophyllenyl), spiropentanyl, diclyclopentanespiranyl, decalinyl, phenyl, benzyl, naphthyl, indenyl, 2H-indenyl, azulenyl, phenanthryl, anthryl, fluorenyl, acenaphthylenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The term "heterocycle" includes both aromatic (heteroaryl) and non-aromatic heterocyclic rings non-limiting examples of which include: pyrrolyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrazolyl, 2H-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazoyl, 1,2,4-oxadiazolyl, 2H-pyranyl, 4H-pyranyl, 2H-pyran-2-one-yl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, s-triazinyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, oxepinyl, 4H-1,2-diazepinyl, indenyl 2H-indenyl, benzofuranyl, isobenzofuranyl, indolyl, 3H-indolyl, 1H-indolyl, benzoxazolyl, 2H-1-benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, 2H-1,4-benzoxazinyl, pyrrolidinyl, pyrrolinyl, quinoxalinyl, furanyl, thiophenyl, benzimidazolyl, and the like each of which can be substituted or unsubstituted.

An example of a unit defined by the term "alkylenearyl" is a benzyl unit having the formula:



whereas an example of a unit defined by the term "alkyleneheteroaryl" is a 2-picolyl unit having the formula:



The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "encompassing moieties or units which can replace a hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety. Also substituted can include replacement of hydrogen atoms on two adjacent carbons to form a new moiety or unit." For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. An epoxide unit is an example of a substituted unit which requires replacement of a hydrogen atom on adjacent carbons. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain, can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit." The following are non-limiting

examples of units which can serve as a replacement for hydrogen atoms when a hydrocarbyl unit is described as "substituted."

i) $-[C(R^{12})_2]_p(CH=CH)_qR^{12}$; wherein p is from 0 to 12; q is from 0 to 12;

ii) $-C(Z)R^{12}$;

iii) $-C(Z)_2R^{12}$;

iv) $-C(Z)CH=CH_2$;

v) $-C(Z)N(R^{12})_2$;

vi) $-C(Z)NR^{12}N(R^{12})_2$;

vii) -CN;

viii) -CNO;

ix) $-CF_3$, $-CCl_3$, $-CBr_3$;

Z) $-N(R^{12})_2$;

xi) $-NR^{12}CN$;

xii) $-NR^{12}C(Z)R^{12}$;

xiii) $-NR^{12}C(Z)N(R^{12})_2$;

xiv) $-NHN(R^{12})_2$;

xv) $-NHOR^{12}$;

xvi) -NCS;

xvii) $-NO_2$;

xviii) $-OR^{12}$;

xix) -OCN;

xx) $-OCF_3$, $-OCCl_3$, $-OCBr_3$;

xxi) -F, -Cl, -Br, -I, and mixtures thereof;

xxii) -SCN;

xxiii) $-SO_3M$;

xxiv) $-OSO_3M$;

xxv) $-SO_2N(R^{12})_2$;

xxvi) $-SO_2R^{12}$;

xxvii) $-P(O)H_2$;

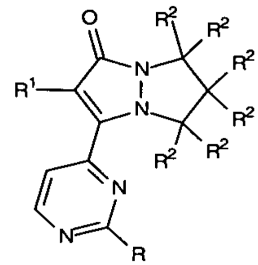
xxviii) $-PO_2$;

xxix) $-P(O)(OH)_2$;

xxx) and mixtures thereof;

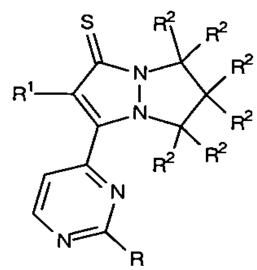
wherein R^{12} is hydrogen, substituted or unsubstituted C_1-C_{20} linear, branched, or cyclic alkyl, C_6-C_{20} aryl, C_7-C_{20} alkylenearyl, and mixtures thereof; M is hydrogen, or a salt forming cation; Z is =O, =S, $=NR^{11}$, and mixtures thereof. Suitable salt forming cations include, sodium, lithium, potassium, calcium, magnesium, ammonium, and the like.

The first aspect of the present invention relates to compounds having the formula:



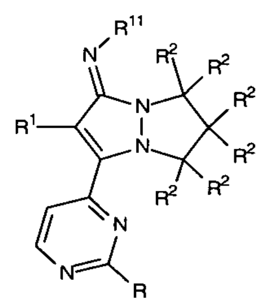
which are 2-R^1-substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2a]pyrazol-1-ones.

The second aspect of the present invention relates to compounds having the formula:



which are 2-R^1substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2a]pyrazol-1-thiones.

The third aspect of the present invention relates to compounds having the formula:



which are 2-R^1substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2a]pyrazol-1-ylideneamines and derivatives thereof.

R is a substituent at the 2-position of the pyrimidin-4-yl portion of the general scaffold, said R unit is:

a) an ether having the formula $-O[CH_2]_kR^3$; or

b) a primary or secondary amino unit having the formula $-NR^{4a}R^{4b}$;

wherein R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted cyclic hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl or alkylenearyl, substituted or unsubstituted heteroaryl or alkyleneheteroaryl; the index k is from 0 to 5.

The following are the various aspects of R units according to the present invention wherein R is an ether having the formula $-O[CH_2]_kR^3$. However, the formulator is not limited to the herein exemplified iterations and examples.

A) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 0) and R^3 is substituted or unsubstituted aryl.

   i) One iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following non-limiting example of R: phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,4-difluorophenoxy, 3-trifluoromethylphenoxy, 4-trifluoromethylphenoxy, 2,4-trifluoromethyl phenoxy, and the like.

   ii) Another iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following non-limiting examples: 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 4-ethylphenoxy, and the like.

   iii) A further iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following non-limiting examples: (2-methyoxy)phenoxy, (3-methoxy)phenoxy, (4-methoxy)phenoxy, 3-[(N-acetyl)amino]phenoxy, 3-benzo[1,3]dioxol-5-yl, and the like.

B) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 0) and R^3 is substituted or unsubstituted heteroaryl.

   i) A first iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

   ii) A second iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted heteroaryl. This iteration includes the following non-limiting examples: 2-aminopyrimidin-4-yl, and the like.

C) R units encompassing ethers having the formula $-OCH_2R^3$ (the index k equal to 1) and R^3 is substituted or unsubstituted aryl.

   i) A first iteration of this aspect of R comprises ethers having the formula $-OCH_2R^3$ and R^3 is substituted or unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, 2-aminopyrimidin-4-yl, 4-aminopyrimidin-6-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

   ii) A second iteration of this aspect of R wherein R is an ether having the formula $-OCH_2R^3$ and R^3 is substituted or unsubstituted alkyleneheteroaryl-aryl. This

iteration includes the following non-limiting examples: pyridin-3-ylethyl, (2-methyl-2-pyridin-3-yl)ethyl, and the like.

D) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 1) and R^3 is R^3 is substituted or unsubstituted C_1-C_4 alkyl.

i) A first iteration of this aspect of R is an ether having the formula $-OR^3$ and R^3 is unsubstituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: methyl, ethyl, isopropyl, (*S*)–1-methypropyl, and the like.

ii) A second iteration of this aspect of R is an ether having the formula $-OR^3$ and R^3 is a substituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: 2-methoxyethyl, (*S*)–1-methy-3-methyoxypropyl, and the like.

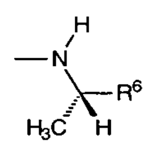
The following are the various aspects of R units according to the present invention wherein R is an amine having the formula $-NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_mR^6$;

each R^{5a} and R^{5b} are independently hydrogen, or C_1-C_4 linear, branched, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; cyclic alkyl, and mixtures thereof; R^6 is hydrogen, substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$, R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index m is from 0 to 5. However, the formulator is not limited to the herein exemplified iterations and examples.

A) R units encompassing chiral amino groups wherein R^{4a} is hydrogen, R^{5a} is hydrogen and R^{5b} is methyl, said units having the formula:



and the indicated stereochemistry.

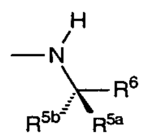
i) A first iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted phenyl. This iteration includes the following non-limiting examples: (S)-1-methyl-1-phenylmethylamino, (S)-1-methyl-1-(4-fluorophenyl)methylamino, (S)-1-methyl-1-(4-methylphenyl)methyl-amino, (S)-1-methyl-1-(4-methoxyphenyl)methylamino, (S)-1-methyl-1-(2-aminophenyl)methylamino, (S)-1-methyl-1-(4-aminophenyl)methylamino, and the like.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted heteroaryl. This iteration includes the following non-limiting examples: (S)-1-methyl-1-(pyridin-2-yl)methylamino, (S)-1-methyl-1-

(pyridin-3-yl)methylamino, (S)-1-methyl-1-(pyridin-4-yl)methylamino, (S)-1-methyl-1-(furan-2-yl)methylamino, (S)-1-methyl-1-(3-benzo[1,3]dioxol-5-yl)methylamino, and the like.

iii) A third iteration of this aspect of R is an amine comprising an R^6 which is C_1-C_4 substituted or unsubstituted alkyl. This iteration includes the following non-limiting examples: (*S*)-1-methylpropylamino, (*S*)-1-methyl-2-(methoxy)ethylamino.

B) R units encompassing chiral amino groups wherein R^{4a} is hydrogen, R^{5a} and R^{5b} are each C_1-C_4 alkyl, said units having the formula:

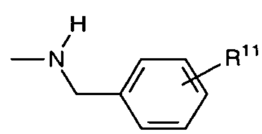


and the indicated stereochemistry when R^{5a}, R^{5b} and R^6 are not the same.

i) A first iteration of this aspect of R is an amine which does not have a chiral center, non-limiting examples of which includes 1,1-dimethylethylamine, 1,1-dimethylbenzylamine and the like.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted C_1-C_4 alkyl. This iteration includes the following non-limiting examples: (S)-1-methyl-2-hydroxy-2-methylpropylamine, (S)-1-methyl-2-hydroxy-2-methylbutylamine, and the like.

C) R units encompassing alkylenearyl amines wherein R^{4a} is hydrogen, both R^{5a} and R^{5b} of R^{4b} are hydrogen, R^6 is substituted or unsubstituted aryl, said unit having the formula:

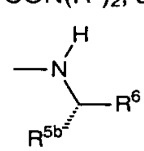


wherein R^{11} is hydrogen or a "substituted unit" as defined herein above.

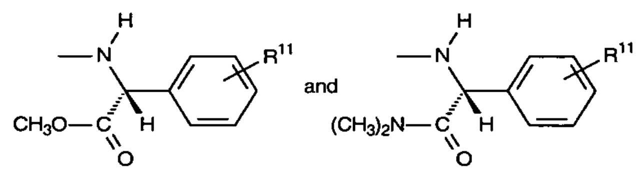
i) A first iteration of this aspect comprises the following non-limiting examples of R units: benzylamino, (2-aminophenyl)methylamino; (4-fluorophenyl)methylamino, (4-methoxyphenyl)methylamino; (4-propanesulfonylphenyl)methylamino; and the like.

ii) A second iteration of this aspect comprises the following non-limiting examples of R units: (2-methylphenyl)methylamino; (3-methylphenyl)-methylamino; (4-methylphenyl)methylamino; and the like.

D) R units encompassing amines wherein R^{4a} is hydrogen, R^{4b} comprises R^{5a} equal to hydrogen and R^{5b} equal to $-CO_2R^7$ or $-CON(R^7)_2$; said unit having the formula:

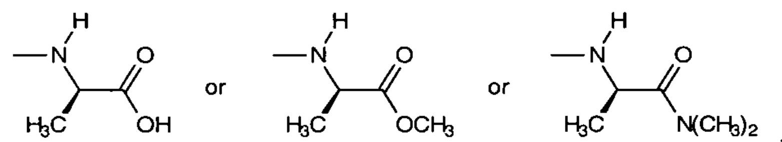


i) A first iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted phenyl. This iteration includes the following non-limiting examples:



wherein R^{11} is hydrogen or a "substitute" as defined herein above.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted alkyl. This iteration includes the following non-limiting examples:



R^1 units are selected from:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl.

The first aspect of R^1 units encompasses halogen substituted phenyl units, non-limiting examples of which include 4-fluorophenyl, 2,4-difluorophenyl, 4-chlorophenyl, and the like.

Each R^2 unit is independently selected from the group consisting of:

a) hydrogen;

b) $-(CH_2)_jO(CH_2)_nR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

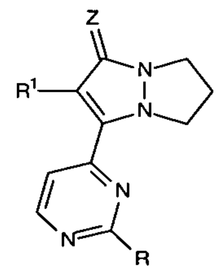
g) $-(CH_2)_jOCON(R^{10})_2$;

h) two R^2 units can be taken together to form a carbonyl unit;

i) and mixtures thereof;

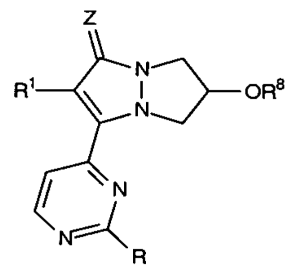
R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5, n is an index from 0 to 5.

The first aspect of the present invention relating to R^2 encompasses scaffolds having the formula:



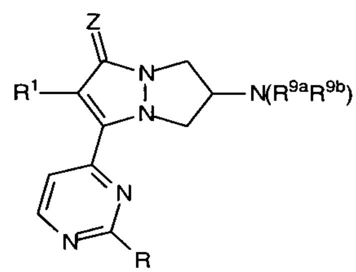
wherein each R^2 unit is hydrogen.

A second aspect relates to scaffolds having the formula:



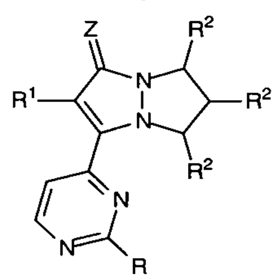
wherein R^8 is hydrogen or C_1-C_4 alkyl.

A third aspect relates to scaffolds having the formula:



wherein R^{9a} and R^{9b} are each independently hydrogen, methyl, or R^{9a} and R^{9b} can be taken together to form a piperidine or morpholine ring.

A fourth aspect relates to scaffolds having the formula:

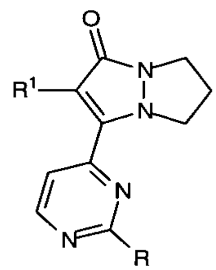


wherein one R^2 is $-CO_2R^{10}$ and the other R^2 units are hydrogen; one R^{10} is hydrogen or methyl.

Z is O, S, NR^{11}, or NOR^{11}; R^{11} is hydrogen or C_1-C_4 alkyl. The first aspect of the present invention as it relates to Z units, comprises oxygen atoms which provide 2-R^1substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-ones, the second aspect relates to Z units comprising sulfur atoms which provide 2-R^1substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2a]pyrazol-1-thiones, and the third aspect of the present invention

as it relates to Z units, comprises NR^{11} units thereby providing 2-R^1substituted-3-(2-R-substituted-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2a]pyrazol-1-ylideneamines and derivatives thereof.

The first category of inflammatory cytokine release inhibiting compounds according to the present invention have the general scaffold having the formula:



wherein R units are ethers having the formula $-OR^3$, wherein R^1 and R^3 are described herein below in Table I

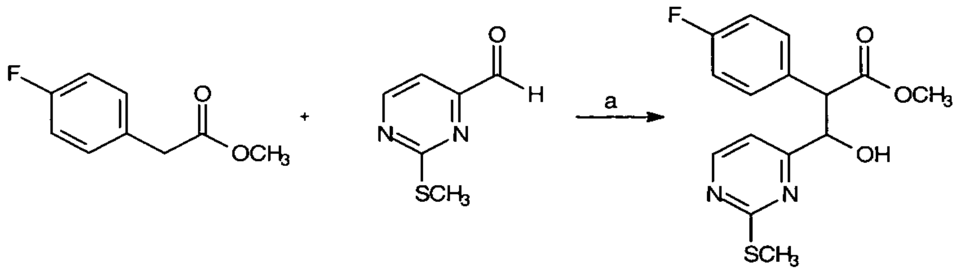
TABLE I

No.	R^1	R
1	4-fluorophenyl	phenoxy
2	4-fluorophenyl	2-fluorophenoxy
3	4-fluorophenyl	3-fluorophenoxy
4	4-fluorophenyl	4-fluorophenoxy
5	4-fluorophenyl	2,6-difluorophenoxy
6	4-fluorophenyl	2-cyanophenoxy
7	4-fluorophenyl	3-cyanophenoxy
8	4-fluorophenyl	2-trifluoromethylphenoxy
9	4-fluorophenyl	4-trifluoromethylphenoxy
10	4-fluorophenyl	N-methylpiperadin-4-yl
11	4-fluorophenyl	4-methylphenoxy
12	4-fluorophenyl	2,4-dimethylphenoxy
13	4-fluorophenyl	3-N-acetylaminophenoxy
14	4-fluorophenyl	pyran-4-yloxy
15	4-fluorophenyl	4-methoxyphenoxy
16	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
17	2,4-difluorophenyl	phenoxy
18	2,4-difluorophenyl	2-fluorophenoxy
19	2,4-difluorophenyl	3-fluorophenoxy
20	2,4-difluorophenyl	4-fluorophenoxy
21	2,4-difluorophenyl	2,6-difluorophenoxy

22	2,4-difluorophenyl	2-cyanophenoxy
23	2,4-difluorophenyl	3-cyanophenoxy
24	2,4-difluorophenyl	2-trifluoromethylphenoxy
25	2,4-difluorophenyl	4-trifluoromethylphenoxy
26	2,4-difluorophenyl	N-methylpiperadin-4-yl
27	2,4-difluorophenyl	4-methylphenoxy
28	2,4-difluorophenyl	2,4-dimethylphenoxy
29	2,4-difluorophenyl	3-N-acetylaminophenoxy
30	2,4-difluorophenyl	pyran-4-yloxy
31	2,4-difluorophenyl	4-methoxyphenoxy
32	2,4-difluorophenyl	3-benzo[1,3]dioxol-5-yl
33	3-trifluoromethylphenyl	phenoxy
34	3-trifluoromethylphenyl	2-fluorophenoxy
35	3-trifluoromethylphenyl	3-fluorophenoxy
36	3-trifluoromethylphenyl	4-fluorophenoxy
37	3-trifluoromethylphenyl	2,6-difluorophenoxy
38	3-trifluoromethylphenyl	2-cyanophenoxy
39	3-trifluoromethylphenyl	3-cyanophenoxy
40	3-trifluoromethylphenyl	2-trifluoromethylphenoxy
41	3-trifluoromethylphenyl	4-trifluoromethylphenoxy
42	3-trifluoromethylphenyl	N-methylpiperadin-4-yl
43	3-trifluoromethylphenyl	4-methylphenoxy
44	3-trifluoromethylphenyl	2,4-dimethylphenoxy
45	3-trifluoromethylphenyl	3-N-acetylaminophenoxy
46	3-trifluoromethylphenyl	pyran-4-yloxy
47	3-trifluoromethylphenyl	4-methoxyphenoxy
48	3-trifluoromethylphenyl	3-benzo[1,3]dioxol-5-yl

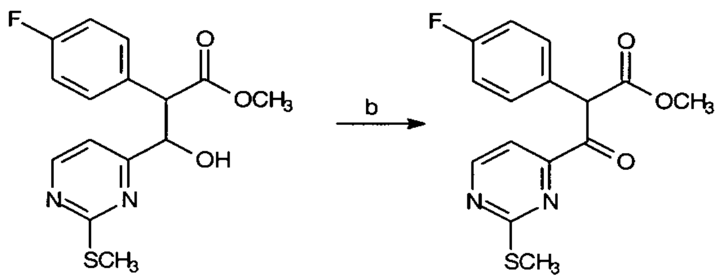
The analogs 1-48 and others like them which comprise this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenylacetate.

General Scheme for Intermediate Type I



1 2

Reagents and conditions: (a) LDA, THF; -78 °C, 1 hr.



2 3

Reagents and conditions: (b) CrO_3, CH_2Cl_2; rt 16 hr.

EXAMPLE 1

2-(4-Fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester (3)

The following is a procedure for the preparation of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, 1, adapted from the procedure of H. Bredereck et al., *Chem. Ber.*, **97**, pp 3407-3417 (1964) included herein by reference.

To a 12 L 3-neck flask under inert atmosphere is charged N,N-dimethyl-formamide dimethyl acetyl (801 g) and pyruvic aldehyde dimethyl acetal (779 g). The mixture is heated to reflux for 18 hours during which time the temperature decreases from about 109 °C to about 80 °C. The solution is cooled and methanol (4 L) is added to dissolve the crude residue. The solution is then cooled to 20 °C and thiourea (892 g, 11.7 mol) is added. After allowing the mixture to stir about 15 minutes, sodium methoxide (741 g, 13.7 mol) is added in 4 equal portions over 1 hour while maintaining the solution temperature in the range of 18 – 28 °C. The mixture is stirred for 5 hours at room temperature, cooled to 20 °C, then methyl iodide (2 kg) is added over 1.25 hours while maintaining the reaction temperature in the range of 17 – 29 °C. Stirring is continued for 18 hours at room temperature. The methanol and unreacted methyl iodide is removed by heating the solution at 35 °C @ 40 torr to produce about 4.46 kg of a dark residue which is partitioned between 14 L of water and 5 L of ethyl acetate. The water fraction is extracted a

second time with ethyl acetate, the organic layers combined and concentrated *in vacuo* too afford 685 g of an oil which is purified over silica to 522 g of 4-dimethoxymethyl-2-methylsulfanyl-pyrimidine.

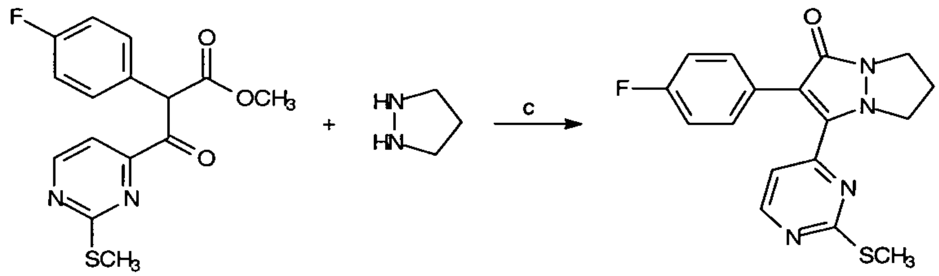
The dimethyl acetal obtained above is then hydrolyzed to the free aldehyde by heating to 60 °C for 3 hours in 1 M HCl. Workup for neutral using ethyl acetate to extract the product affords 347 g crude product which is purified over silica to afford 401 g of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, **1**.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester (2): To a cold (-78 °C) solution of lithium diisopropylamide (21.4 mL of 2M solution in THF, 42.8 mmol) in THF (70 mL) is added dropwise a solution of methyl 4-fluorophenyl-acetate (6.0 g, 35.7 mmol) in THF (30 mL). The solution is stirred for 1 hour at –78 °C after which a solution of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, **1**, (6.0 g, 39.3 mmol) in THF (30 mL) is added dropwise to the reaction mixture. Stirring is continued for 45 minutes at –78 °C then the reaction is quenched by pouring the reaction solution into aqueous saturated NH_4Cl. The aqueous phase is extracted with ethyl acetate. The organic phases combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue is purified over silica (33%EtOAc/hexanes) to afford 8.7 g (76%) of the desired product as a mixture (1:1) of diastereomers.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester (3): To a suspension of CrO_3 in CH_2Cl_2 (300 mL) is added pyridine. The mixture is stirred vigorously for 1 hour at room temp. A solution of the crude 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester, **2**, prepared above in CH_2Cl_2 (50 mL) is added dropwise to the chromium suspension. The reaction mixture is stirred at room temperature for 16 hours, diluted with ether (1 L) and filtered through a pad of Celite. The filtrate is concentrated *in vacuo* and the resulting residue is purified over silica (25% EtOAc/hexanes) to afford 3.7 g (43% yield) of the desired product as a yellow solid.

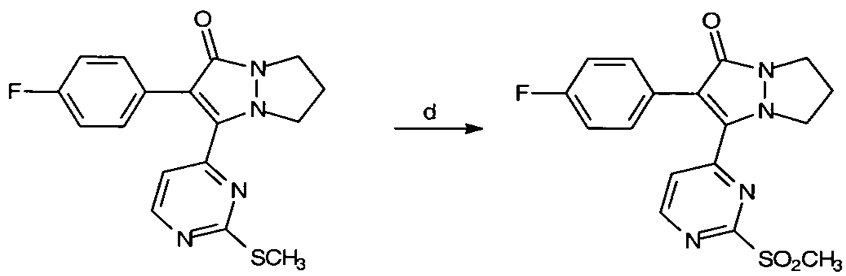
The following example relates to the formation of 6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one ring systems utilizing pyrazolidine, however the formulator may utilize substituted cyclic hydrazine reagents to achieve other scaffolds having R^2 ring units which are not hydrogen, *inter alia*, 3-methylpyrazolidine.

General Scheme for Intermediate Type II



3 4

Reagents and conditions: (c) pyridine; 90 °C, 16 hr.



4 5

Reagents and conditions: (d) Oxone®, MeOH/THF/H_2O; rt 1 hr.

EXAMPLE 2

2-(4-Fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one (5)

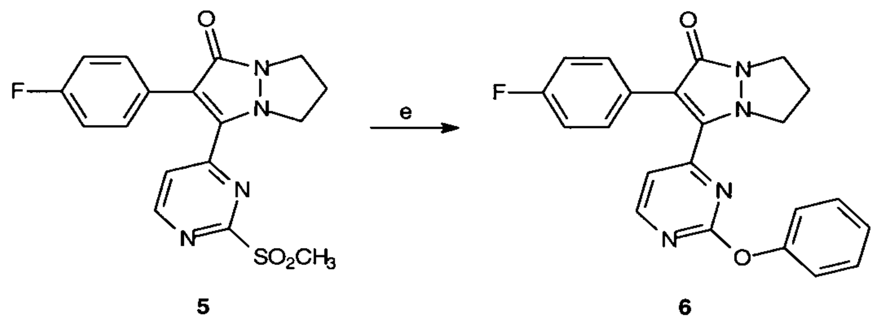
Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one (4): To a solution of pyrazolidine (7.8 g, 54.16 mmol) in pyridine (100 mL) is added 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester, **3**, (11.5 g, 36.1 mmol). The reaction mixture is heated to 90 °C for 16 hours. The solvent is removed *in vacuo* and the resulting residue purified over silica (100% EtOAc, followed by 10% MeOH/EtOAc) to afford 3.9 g (37% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one (5): To a solution of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one, **4**, (1.3 g, 3.8 mmol) in THF:methanol (56 mL of a 1:1 mixture) is added dropwise a solution of Oxone® (potassium peroxymonosulfate) (9.34 g, 15.2 mmol) in water (42 mL). The reaction is stirred 1 hour at room temperature, diluted with aqueous $NaHCO_3$ and extract three times with ethyl acetate. The organic layers are combined, dried, and concentrated *in vacuo* too afford the crude desired product which is used without further purification.

The following is a procedure wherein Intermediate Type II compounds can be utilized for preparation of the inflammatory cytokine release inhibitors of Category I.

EXAMPLE 3

2-(4-Fluorophenyl)-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one (6)



Reagents and conditions: (e) phenol, NaH, THF, 1.5 hr rt.

Preparation of 2-(4-fluorophenyl)-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one (6): To a solution of phenol (0.66 g, 7.08 mmol) in THF (5 mL) is added NaH (0.24 g, 5.91 mmol) followed by a solution of the crude 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one, **5**, prepared herein above (0.25 g, 0.67 mmol) in THF (2 mL). The reaction mixture is stirred for 1.5 hours at room temperature, diluted with aqueous $NaHCO_3$ and extracted with twice with ethyl acetate. The organic layers are combined, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product which is purified over silica (100% EtOAc, followed by 10% MeOH/EtOAc) to provide 0.35 g (38% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 5.1 Hz, 1H), 7.49 (dd, J = 7.8, 7.8 Hz, 2H), 7.40 (ddd, J = 5.4, 5.4 Hz, 2H), 7.35-7.22 (m, 3H), 7.10 (dd, J = 8.4, 8.4 Hz, 2H), 6.90 (d, J = 6.8 Hz, 1H), 4.05 (t, J = 7.2 Hz, 2H), 3.86 (t, J = 7.2 Hz, 2H), 2.59 (dt, J = 7.2, 7.2 Hz, 2H); HRMS calcd for $C_{22}H_{18}FN_4O_2$ $(M + H)^+$ 389.1414; found 389.1407. This compound corresponds to analog 1 from Table I.

The following compounds from the first aspect of Category I can be prepared by the procedure described herein above.

N-(3-{4-[2-(4-Fluoro-phenyl)-3-oxo-6,7-dihydro-3H,5H-pyrazolo[1,2-a]pyrazol-1-yl]-pyrimidin-2-yloxy}-phenyl)-acetamide; ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.11 (s, 1H), 8.66 (d, J = 5.1 Hz, 1H), 7.64 (m, 1H), 7.41-7.34 (m, 4H), 7.17 (t, J = 9.0 Hz, 2H), 7.02 (d, J = 5.1 Hz, 6.92-

6.80 (m, 1H), 3.84 (t, J = 6.9 Hz, 2H), 3.81 (t, J = 6.9 Hz, 2H), 2.46 (m, 2H), 2.06 (s, 3H); HRMS calcd for $C_{24}H_{20}FN_5O_3$ $(M + H)^+$ 446.1628; found 446.1606.

2-(4-Fluorophenyl)-3-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, J = 5.4, 1.5 Hz, 1H), 7.43-7.38 (m, 2H), 7.14-7.00 (m, 5H), 6.88 (dd, J = 5.1, 1.5 Hz, 1H), 4.02 (t, J = 7.2 Hz, 2H), 3.86 (t, J = 7.2 Hz, 2H), 2.59 (dt, J = 7.2, 7.2 Hz, 2H), 2.38 (s, 3H), 2.19 (s, 3H); HRMS calcd for $C_{24}H_{21}FN_4O_2$ $(M + H)^+$ 417.1727; found 417.1727.

2-(2,4-Difluorophenyl)-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 5.1 Hz, 1H), 7.60-7.46 (m, 3H), 7.33 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.01 (t, J = 8.1 Hz, 1H0, 6.91-6.83 (m, 2H), 4.09 (t, J = 6.6 Hz, 2H), 3.92 (t, J = 6.9 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H): MS $(M + H)^+$ 407.2.

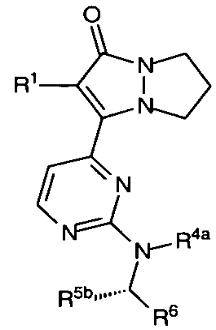
2-(4-fluorophenyl)-3-[2-(4-fluorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 5.1 Hz, 1H), 7.39 (dd, J = 8.7, 5.4 Hz, 2H), 7.21-7.10 (m, 5H), 6.91 (d, J = 5.1 Hz, 1H), 4.42-4.35 (m, 2H), 4.10-4.04 (t, J = 7.2 Hz, 2H), 2.71 (dt, J = 7.2, 7.2 Hz, 2H);MS $(M + H)^+$ 406.9.

2-(4-Fluorophenyl)-3-[2-(2,6-difluorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 5.1 Hz, 1H), 7.41 (dd, J = 8.7, 5.4 Hz, 2H), 7.15-7.07 (m, 5H), 6.98 (d, J = 5.1 Hz, 1H), 4.31 (t, J = 8.2 Hz, 2H), 4.09 (t, J = 8.2 Hz, 2H), 2.70 (dt, J = 8.2, 8.2 Hz, 2H); MS $(M + H)^+$ 425.2.

2-(4-Fluorophenyl)-3-[2-(2-fluorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 5.1 Hz, 1H), 7.41-7.23 (m, 6H), 7.11 (t, J = 8.7 Hz, 2H), 6.94 (d, J = 5.1 Hz, 1H), 4.27 (t, J = 8.2 Hz, 2H), 4.00 (t, J = 8.2 Hz, 2H), 2.66 (dt, J = 8.2, 8.2 Hz, 2H); MS $(M + H)^+$ 407.2.

2-(4-Fluorophenyl)-3-[2-(3-fluorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 5.1 Hz, 1H), 7.49-7.38 (m, 3H), 7.11 (t, J = 8.7 Hz, 2H), 7.04-6.98 (m, 3H), 6.94 (d, J = 5.1 Hz, 1H), 4.13 (t, J = 6.9 Hz, 2H), 3.97 (t, J = 6.9 Hz, 2H), 2.66 (dt, J = 6.9, 6.9 Hz, 2H); MS $(M + H)^+$ 406.9.

A second aspect of the Category I inflammatory cytokine release inhibiting compounds according to the present invention have the general scaffold having the formula:



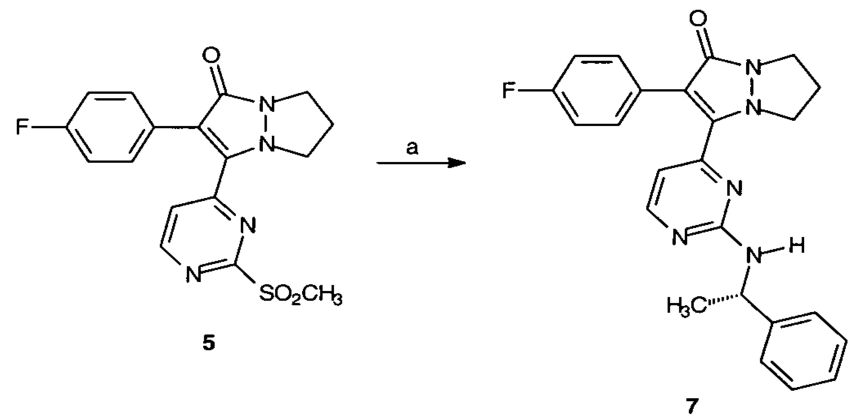
wherein R units are amines having the formula $-NR^{4a}[CHR^{5b}]R^6$, and R^1, R^{4a}, R^{5b}, and R^6 are described herein below in Table II. The stereochemistry of R^{5b} is the configuration shown when R^{5b} or R^6 is not hydrogen.

TABLE II

No.	R^1	R^{4a}	R^{5b}	R^6
49	4-fluorophenyl	H	H	phenyl
50	4-fluorophenyl	H	H	4-fluorophenyl
51	4-fluorophenyl	H	H	2-aminophenyl
52	4-fluorophenyl	H	H	2-methylphenyl
53	4-fluorophenyl	H	H	4-methylphenyl
54	4-fluorophenyl	H	H	4-methoxyphenyl
55	4-fluorophenyl	H	H	4-(propanesulfonyl)phenyl
56	4-fluorophenyl	H	H	3-benzo[1,3]dioxol-5-yl
57	4-fluorophenyl	H	H	pyridin-2-yl
58	4-fluorophenyl	H	H	pyridin-3-yl
59	4-fluorophenyl	H	methyl	phenyl
60	4-fluorophenyl	H	methyl	4-fluorophenyl
61	4-fluorophenyl	H	methyl	2-aminophenyl
62	4-fluorophenyl	H	methyl	2-methylphenyl
63	4-fluorophenyl	H	methyl	4-methylphenyl
64	4-fluorophenyl	H	methyl	4-methoxyphenyl
65	4-fluorophenyl	H	methyl	4-(propanesulfonyl)phenyl
66	4-fluorophenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
67	4-fluorophenyl	H	methyl	pyridin-2-yl
68	4-fluorophenyl	H	methyl	pyridin-3-yl
69	4-fluorophenyl	H	H	H
70	4-fluorophenyl	H	H	methyl
71	4-fluorophenyl	H	H	ethyl

72	4-fluorophenyl	H	H	vinyl
73	4-fluorophenyl	H	H	cyclopropyl
74	4-fluorophenyl	H	H	cyclohexyl
75	4-fluorophenyl	H	H	methoxymethyl
76	4-fluorophenyl	H	H	methoxyethyl
77	4-fluorophenyl	H	H	1-hydroxy-1-methylethyl
78	4-fluorophenyl	H	H	$-CO_2H$
79	4-fluorophenyl	H	methyl	H
80	4-fluorophenyl	H	methyl	methyl
81	4-fluorophenyl	H	methyl	ethyl
82	4-fluorophenyl	H	methyl	vinyl
83	4-fluorophenyl	H	methyl	cyclopropyl
84	4-fluorophenyl	H	methyl	cyclohexyl
85	4-fluorophenyl	H	methyl	methoxymethyl
86	4-fluorophenyl	H	methyl	methoxyethyl
87	4-fluorophenyl	H	methyl	1-hydroxy-1-methylethyl
88	4-fluorophenyl	H	methyl	$-CO_2H$
89	3-trifluoromethylphenyl	H	methyl	phenyl
90	3-trifluoromethylphenyl	H	methyl	4-fluorophenyl
91	3-trifluoromethylphenyl	H	methyl	2-aminophenyl
92	3-trifluoromethylphenyl	H	methyl	2-methylphenyl
93	3-trifluoromethylphenyl	H	methyl	4-methylphenyl
94	3-trifluoromethylphenyl	H	methyl	4-methoxyphenyl
95	3-trifluoromethylphenyl	H	methyl	4-(propanesulfonyl)phenyl
96	3-trifluoromethylphenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
97	3-trifluoromethylphenyl	H	methyl	pyridin-2-yl
98	3-trifluoromethylphenyl	H	methyl	pyridin-3-yl
99	3-trifluoromethylphenyl	H	methyl	H
100	3-trifluoromethylphenyl	H	methyl	methyl
101	3-trifluoromethylphenyl	H	methyl	ethyl
102	3-trifluoromethylphenyl	H	methyl	vinyl
103	3-trifluoromethylphenyl	H	methyl	cyclopropyl
104	3-trifluoromethylphenyl	H	methyl	cyclohexyl
105	3-trifluoromethylphenyl	H	methyl	methoxymethyl
106	3-trifluoromethylphenyl	H	methyl	methoxyethyl
107	3-trifluoromethylphenyl	H	methyl	1-hydroxy-1-methylethyl
108	3-trifluoromethylphenyl	H	methyl	$-CO_2H$

Utilizing intermediates such as compound **5**, as a convenient starting point the analogs 49-108 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenylacetate.



Reagents and conditions: (a) (S)-(α)-methylbenzylamine, toluene, 140 °C, 12 hr.

EXAMPLE 4

<u>2-(4-Fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (7)</u>

Preparation of 2-(4-fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (7): A solution of the crude 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one, **5**, prepared herein above (0.86 g, 2.3 mmol) and (*S*)-(-)-α-methyl-benzyl amine (10.5 mL, 81.6 mmol) is dissolved in toluene (18 mL). The resulting mixture is heated to 140 °C for 12 hours, cooled to room temperature and the solvent removed *in vacuo*. The resulting residue is purified over silica (1:1 EtOAc/hexanes) to afford the desired product which to analog 59 from Table II. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 7.42-7.34 (m, 7H), 7.04 (ddd, *J* = 9.0, 6.9, 2.1 Hz, 2H), 6.39 (d, *J* = 5.1 Hz, 1H), 5.68 (bd s, 1H), 5.10 (m, 1H), 3.97 (dt, *J* = 7.5, 7.5, 7.5 Hz, 2H), 2.45 (bd s, 2H), 1.67 (m, 2H), 1.60 (d, *J* = 7.5 Hz, 3H); HRMS calcd for $C_{24}H_{22}FN_5O$ $(M + H)^+$ 416.1887; found 416.1897.

The following compounds from the second aspect of Category I can be prepared by the procedure described herein above.

2-(4-Fluorophenyl)-3-[2-(N'-methyl-N'-phenylhydrazino)-pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.40 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.29-7.25 (m, 2H), 7.06 (dd, *J* = 8.4, 8.4 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.85 (t, 7.8 Hz, 1H), 6.57 (d, *J* = 5.1 Hz, 1H), 4.00 (t, *J* = 6.9 Hz, 4H), 3.39 (s, 3H), 2.48-2.33 (m, 2H); MS $(M + H)^+$ 417.2.

(*R*)-{4-[2-(4-Fluorophenyl)-3-oxo-6,7-dihydro-3*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-yl]-pyrimidin-2-ylamino}-phenylacetic acid methyl ester; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 7.54-7.24 (m, 7H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 4.8 Hz, 1H), 5.65-5.58 (m, 2H), 4.05-4.00 (m, 2H), 3.79 (s, 3H), 3.78-3.68 (m, 2H), 1.67 (m, 2H); MS $(M + H)^+$ 460.0.

2-(4-Fluorophenyl)-3-(2-benzylaminopyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 4.5 Hz, 1H), 7.45-7.29 (m, 9H), 7.06 (dd, *J* = 9.0, 8.4 Hz, 2H), 6.47 (d, *J* = 5.4 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 2H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.80-3.65 (m, 2H), 2.65-2.52 (m, 2H); MS $(M + H)^+$ 402.1.

2-(4-Fluorophenyl)-3-[2-(1-(*S*)-methylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 4.8 Hz, 7.46-7.40 (m, 2H), 7.05 (dt, *J* = 8.7, 2.4 Hz, 2H), 6.38 (dd, *J* = 4.8, 3.0 Hz, 1H), 5.11 (bd s, 1H), 4.13-3.96 (m, 5H), 2.73 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.66-1.55 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); HRMS calcd for $C_{20}H_{22}FN_5O$ $(M + H)^+$ 368.1886; found 386.1880.

2-(4-Fluorophenyl)-3-[2-(allylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 5.1 Hz, 1H), 7.43 (dd, *J* = 9.0, 5.4 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 5.1 Hz, 1H), 6.00 (dddd, *J* = 7.2, 7.2, 7.2, 5.1 Hz, 1H), 5.45 (bd s, 1H), 5.28 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.20 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.13-4.04 (m, 6H), 2.71 (dt, *J* = 7.2, 7.2 Hz, 2H); HRMS calcd for $C_{19}H_{18}FN_5O$ $(M + H)^+$ 352.1573; found 352.1582.

2-(4-Fluorophenyl)-3-{2-[1-(*S*)-(4-methylphenyl)ethylamino]pyrimidin-4-yl}-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 5.4 Hz, 1H), 7.40 (dd, *J* = 8.7, 5.7 Hz, 2H), 7.28-7.27 (m, 2H), 7.17 (d, *J* =7.8 Hz, 2H), 7.04 (t, *J* = 9.0 Hz, 2H), 6.41 (d, *J* = 5.4 Hz, 1H), 5.20 (m, 1H), 4.02-3.96 (m, 4H), 2.52-2.45 (m, 2H), 2.36 (s, 3H), 1.60 (d, *J* = 6.9 Hz, 3H); HRMS calcd for $C_{25}H_{24}FN_5O$ $(M + H)^+$ 430.2043; found 430.2057.

2-(4-Fluorophenyl)-3-[2-(1-(*S*)-cyclohexyl-ethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.8 Hz, 1H), 7.44 (dd, *J* = 9.0, 5.7 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 5.1 Hz, 1H), 5.12 (bd s, 1H), 4.14-4.02 (m,

4H), 3.99-3.92 (m, 1H), 2.73 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.88-1.63 (m, 4H), 1.54-1.40 (m, 1H), 1.28-1.03 (m, 6H), 1.20 (d, *J* = 6.9 Hz, 3H); HRMS calcd for $C_{24}H_{28}FN_5O$ $(M + H)^+$ 421.2279; found 421.2264.

2-(4-Fluorophenyl)-3-[2-(1-(*R*)-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.4 Hz, 1H), 7.43-7.23 (m, 7H), 7.05 (t, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 5.4 Hz, 1H), 5.13 (m, 1H), 4.16-3.94 (m, 2H), 2.58-2.38 (m, 2H), 1.63 (d, J = 6.9 Hz, 3H); MS $(M + H)^+$ 416.0.

2-(4-Fluorophenyl)-3-[2-(*tert*-butylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 5.4 Hz, 1H), 7.43 (dd, *J* = 6.9, 3.3 Hz, 2H), 7.08 (t, *J* = 6.6 Hz, 2H), 6.45 (d, *J* = 5.7 Hz, 1H), 4.12-4.02 (m, 4H), 2.77 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.52 (s, 9H); MS $(M + H)^+$ 368.1

2-(4-Fluorophenyl)-3-[2-(2-hydroxy-1,2-dimethylpropylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (m, 1H), 7.40 (dd, *J* = 9.0, 5.7 Hz, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 5.4 Hz, 1H), 4.24-4.10 (m, 5H), 2.83 (dt, *J* = 8.4, 8.4 Hz, 2H), 1.51-1.36 (m, 9H); MS $(M + H)^+$ 398.1.

2-(4-Fluorophenyl)-3-[(2-cyclopropylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (m, 1H), 7.42 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 5.4 Hz, 1H), 4.27 (m, 2H), 4.15 (t, *J* = 8.4 Hz, 2H), 2.88-2.81 (m, 1H), 2.77 (dt, *J* = 8.4, 8.4 Hz, 2H), 0.93-0.87 (m, 2H), 0.71-0.66 (m, 2H); MS $(M + H)^+$ 352.0.

2-(4-Fluorophenyl)-3-[(2-cyclopropylmethyl)aminopyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ8.17 (d, *J* = 5.1 Hz, 1H), 7.41 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 5.1 Hz, 1H), 5.55 (bd s, 1H), 4.15-4.05 (m, 4H), 3.31 (t, *J* = 5.4 Hz, 2H), 2.78 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.18 (m, 1H), 0.60 (m, 2H), 0.30 (m, 2H); MS $(M + H)^+$ 366.0.

2-(4-Fluorophenyl)-3-[(2-methoxyethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.1 Hz, 1H), 7.42 (dd, J = 8.7, 5.7 Hz, 2H), 7.06 (t, J = 8.7 Hz, 2H), 6.42 (d, J = 5.4 Hz, 1H), 4.20-4.03 (m, 4H), 3.68-3.41 (m, 4H), 3.42 (s, 3H), 2.74 (dt, J = 6.9, 6.9 Hz, 2H); MS $(M + H)^+$ 370.0.

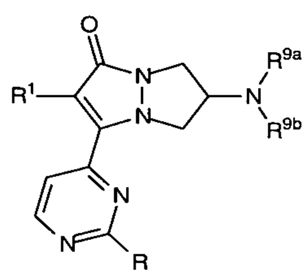
2-(4-Fluorophenyl)-3-[2-(2-methoxy-1-(*S*)-methylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 4.8 Hz, 1H), 7.42 (dd, J = 8.1, 5.4 Hz, 2H), 7.04 (t, J = 8.7 Hz, 2H), 6.39 (d, J = 4.8 Hz, 1H), 5.49 (d, J = 7.8 Hz, 1H), 4.26

(m, 1H), 4.13 (t, J = 6.9 Hz, 2H), 4.06 (t, J = 6.9 Hz, 2H), 3.46 (d, J = 4.8 Hz, 2H), 3.41 (s, 3H), 2.72 (dt, J = 6.9, 6.9 Hz, 2H), 1.30 (s, 3H); MS $(M + H)^+$ 384.0.

2-(4-Fluorophenyl)-3-{2-[1-(*S*)-(4-fluorophenyl)ethylamino]pyrimidin-4-yl}-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 5.1 Hz, 1H), 7.39 (dd, J = 7.8, 5.1 Hz, 2H), 7.07 (t, J = 7.8 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 5.12 (m, 1H), 4.18-3.98 (m, 2H), 2.61-2.45 (m, 2H), 1.64 (d, J = 6.9 Hz, 3H); MS $(M + H)^+$ 433.9.

2-(4-Fluorophenyl)-3-{2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one; ^{1}H NMR (300 MHz, d_6-DMSO) δ8.69-8.51 (m, 2H), 8.22 (d, J = 5.1 Hz, 1H), 7.73-7.68 (m, 1H), 7.42 (dd, J = 8.7, 5.4 Hz, 2H), 7.33-7.26 (m, 1H), 7.04 (t, J = 8.7 Hz, 2H), 6.48 (d, J = 5.1 Hz, 1H), 5.77 (bd s, 1H), 4.69 (d, J = 6.3 Hz, 2H), 4.02 (t, J = 6.9 Hz, 2H), 3.80 (m, 2H), 2.62 (dt, J = 8.7, 8.7 Hz, 2H); MS $(M + H)^+$ 403.1.

The second category of inflammatory cytokine release inhibiting compounds according to the present invention have the general scaffold having the formula:



wherein R units are ethers having the formula $-OR^3$ and R^{9a} and R^{9b} are taken together to form a ring as described herein below in Table III.

TABLE III

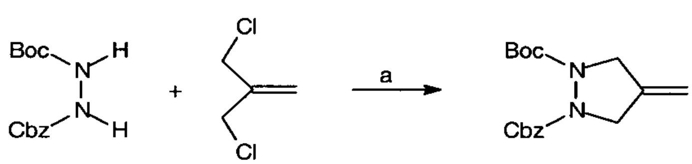
No.	R^1	R^3	R^{9a}/R^{9b} ring
109	4-fluorophenyl	phenoxy	morpholinyl
110	4-fluorophenyl	2-fluorophenoxy	morpholinyl
111	4-fluorophenyl	3-fluorophenoxy	morpholinyl
112	4-fluorophenyl	4-fluorophenoxy	morpholinyl
113	4-fluorophenyl	2,6-difluorophenoxy	morpholinyl
114	4-fluorophenyl	2-cyanophenoxy	morpholinyl
115	4-fluorophenyl	3-cyanophenoxy	morpholinyl
116	4-fluorophenyl	2-trifluoromethylphenoxy	morpholinyl
117	4-fluorophenyl	4-trifluoromethylphenoxy	morpholinyl

118	4-fluorophenyl	2-methylphenoxy	morpholinyl
119	4-fluorophenyl	4-methylphenoxy	morpholinyl
120	4-fluorophenyl	2,4-dimethylphenoxy	morpholinyl
121	4-fluorophenyl	3-N-acetylaminophenoxy	morpholinyl
122	4-fluorophenyl	2-methoxyphenoxy	morpholinyl
123	4-fluorophenyl	4-methoxyphenoxy	morpholinyl
124	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	morpholinyl
125	4-fluorophenyl	phenoxy	piperidin-1-yl
126	4-fluorophenyl	2-fluorophenoxy	piperidin-1-yl
127	4-fluorophenyl	3-fluorophenoxy	piperidin-1-yl
128	4-fluorophenyl	4-fluorophenoxy	piperidin-1-yl
129	4-fluorophenyl	2,6-difluorophenoxy	piperidin-1-yl
130	4-fluorophenyl	2-cyanophenoxy	piperidin-1-yl
131	4-fluorophenyl	3-cyanophenoxy	piperidin-1-yl
132	4-fluorophenyl	2-trifluoromethylphenoxy	piperidin-1-yl
133	4-fluorophenyl	4-trifluoromethylphenoxy	piperidin-1-yl
134	4-fluorophenyl	2-methylphenoxy	piperidin-1-yl
135	4-fluorophenyl	4-methylphenoxy	piperidin-1-yl
136	4-fluorophenyl	2,4-dimethylphenoxy	piperidin-1-yl
137	4-fluorophenyl	3-N-acetylaminophenoxy	piperidin-1-yl
138	4-fluorophenyl	2-methoxyphenoxy	piperidin-1-yl
139	4-fluorophenyl	4-methoxyphenoxy	piperidin-1-yl
140	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	piperidin-1-yl
141	4-fluorophenyl	phenoxy	piperazin-1-yl
142	4-fluorophenyl	2-fluorophenoxy	piperazin-1-yl
143	4-fluorophenyl	3-fluorophenoxy	piperazin-1-yl
144	4-fluorophenyl	4-fluorophenoxy	piperazin-1-yl
145	4-fluorophenyl	2,6-difluorophenoxy	piperazin-1-yl
146	4-fluorophenyl	2-cyanophenoxy	piperazin-1-yl
147	4-fluorophenyl	3-cyanophenoxy	piperazin-1-yl
148	4-fluorophenyl	2-trifluoromethylphenoxy	piperazin-1-yl
149	4-fluorophenyl	4-trifluoromethylphenoxy	piperazin-1-yl
150	4-fluorophenyl	2-methylphenoxy	piperazin-1-yl
151	4-fluorophenyl	4-methylphenoxy	piperazin-1-yl
152	4-fluorophenyl	2,4-dimethylphenoxy	piperazin-1-yl
153	4-fluorophenyl	3-N-acetylaminophenoxy	piperazin-1-yl
154	4-fluorophenyl	2-methoxyphenoxy	piperazin-1-yl

155	4-fluorophenyl	4-methoxyphenoxy	piperazin-1-yl
156	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	piperazin-1-yl
157	4-fluorophenyl	phenoxy	pyrrolidin-1-yl
158	4-fluorophenyl	2-fluorophenoxy	pyrrolidin-1-yl
159	4-fluorophenyl	3-fluorophenoxy	pyrrolidin-1-yl
160	4-fluorophenyl	4-fluorophenoxy	pyrrolidin-1-yl
161	4-fluorophenyl	2,6-difluorophenoxy	pyrrolidin-1-yl
162	4-fluorophenyl	2-cyanophenoxy	pyrrolidin-1-yl
163	4-fluorophenyl	3-cyanophenoxy	pyrrolidin-1-yl
164	4-fluorophenyl	2-trifluoromethylphenoxy	pyrrolidin-1-yl
165	4-fluorophenyl	4-trifluoromethylphenoxy	pyrrolidin-1-yl
166	4-fluorophenyl	2-methylphenoxy	pyrrolidin-1-yl
167	4-fluorophenyl	4-methylphenoxy	pyrrolidin-1-yl
167	4-fluorophenyl	2,4-dimethylphenoxy	pyrrolidin-1-yl
169	4-fluorophenyl	3-N-acetylaminophenoxy	pyrrolidin-1-yl
170	4-fluorophenyl	2-methoxyphenoxy	pyrrolidin-1-yl
171	4-fluorophenyl	4-methoxyphenoxy	pyrrolidin-1-yl
172	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	pyrrolidin-1-yl

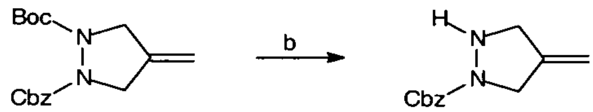
The following is a scheme for preparing compounds belonging to the first aspect of Category II according to the present invention. The first stage encompasses utilization of Type III intermediates to introduce the R^1 unit (4-fluorophenyl in the present example) into the molecule. Intermediate ketones such as compound **11** can be used in the next sequence to introduce the selected amino unit to the 6-position of the pyrazolo[1,2-*a*]pyrazol-1-one ring system.

General Scheme for Intermediate Type III



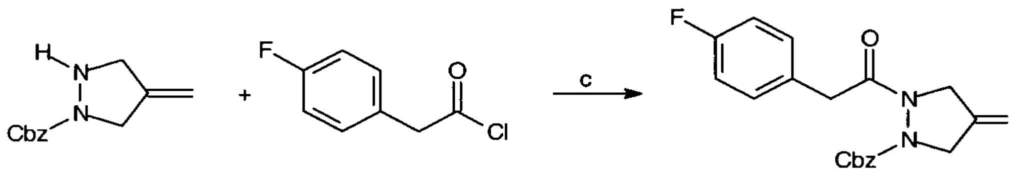
8

Reagents and conditions: (a) NaH, DMF, rt, 12 hr.



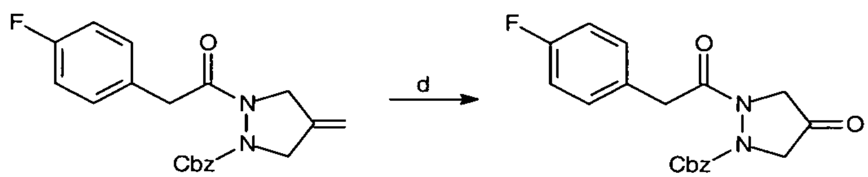
8 **9**

Reagents and Conditions: (b) $SOCl_2$, MeOH, 0 °C to rt, 18 hr



9 **10**

Reagents and Conditions: (c) NaOH, CH_2Cl_2/water, rt 18 hr.



10 **11**

Reagents and Conditions: (d) O_3, CH_2Cl_2, DMS; -78 °C to rt 18 hr.

EXAMPLE 5

<u>2-[2-(4-Fluorophenyl)acetyl]-4-oxo-pyrazolidine-1-carboxylic acid benzyl ester (11)</u>

Preparation of 4-methylenepyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (8): To a suspension of NaH (3.81 g, 95.4 mmol) in DMF (80 mL) is add dropwise a solution of N-Cbz-N'-Boc-hydrazine (12.1 g, 45.4 mmol) in DMF (20 mL). The reaction mixture is stirred about 20 minutes and 3-chloro-2-chloromethyl-propene (5.8 mL, 50 mmol) is added dropwise and the reaction is allowed to stir at room temperature until the reaction is complete by TLC, approximately 12 hours. The reaction solution is partitioned between ethyl acetate and water, the water layer being extracted several times more with solvent. The combined organic layers are dried, filtered, and concentrated to afford the desired product as a clear oil which is used without further purification.

Preparation of 4-methylene-pyrazolidine-1-carboxylic acid 1-benzyl ester (9): To a solution of crude 4-methylenepyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **8**, (30 g) in methanol (300 mL) is added thionyl chloride dropwise at 0 °C. The reaction is warmed to room temperature and stirred an additional 18 hours. Concentration of the reaction *in vacuo*

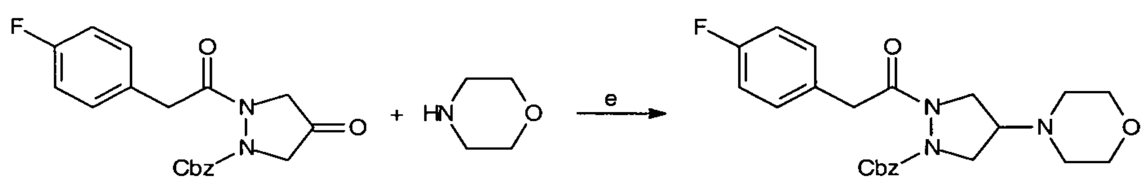
affords a yellow oil which crystallizes upon standing to provide 23 g (97% yield) of the desired product as the HCl salt.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-methylene-pyrazolidine-1-carboxylic acid benzyl ester (10): Sodium hydroxide (0.12 g, 3 mmol) is dissolved in a 1:2 water/methylene chloride solution (30 mL) with rapid stirring followed by the addition of 4-methylene-pyrazolidine-1-carboxylic acid 1-benzyl ester, **9**, (0.62 g, 2.8 mmol) at room temperature. (4-Fluorophenyl)acetyl chloride (0.39 mL, 4.2 mmol) is added and the reaction is allowed to stir for 18 hours after which time the reaction mixture is diluted with water (10 mL) and the layers allowed to separate. The aqueous layer is extracted with methylene chloride, the organic layers combined, dried, and filtered. Concentration *in vacuo* affords the crude product which is purified over silica (1:3 ethyl acetate/hexane) to provide 0.54 g (62 % yield) of the desired product.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-oxo-pyrazolidine-1-carboxylic acid benzyl ester (11): Ozone gas is bubbled into a solution of 2-[2-(4-fluorophenyl)-acetyl]-4-methylene-pyrazolidine-1-carboxylic acid benzyl ester, **10**, (0.28 g, 0.8 mmol) in methylene chloride (15 mL) at –78 °C until the solution retains a blue color. The source of ozone is removed and dimethyl sulfoxide (0.23 mL) is added and the reaction solution allowed to warm to room temperature and stir for 18 hours. The solvent is removed *in vacuo* and the resulting oil purified over silica (1:3 ethyl acetate/hexane) to afford 0.15 g (53 % yield) of the desired product as a clear oil.

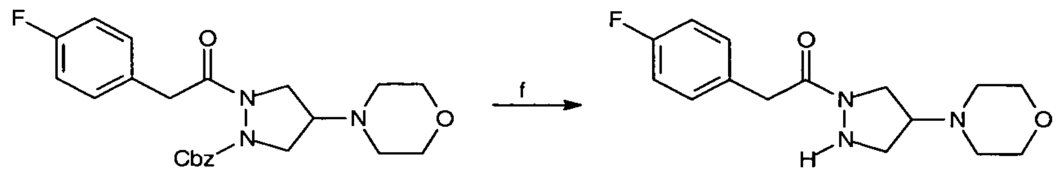
Synthetic intermediates of Type III, for example, compound **11**, can be used as a template for introducing the desired 6-position amino moiety as outlined in the example below.

General Scheme Type IV Intermediates:
Introduction of a 6-amino unit into the scaffold of compounds encompassing the first aspect of Category II analogs.



11 **12**

Reagents and conditions: (e) $Na(OAc)_3BH$, HOAc, THF; rt 12 hr.



12 13

Reagents and conditions: (f) H_2; Pd/C, MeOH.

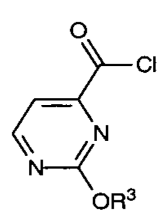
EXAMPLE 6

2-(4-Fluorophenyl)-1-(4-morpholin-4-yl-pyrazolidin-1-yl)-ethanone (13)

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-morpholin-4-yl-pyrazolidine-1-carboxylic acid benzyl ester (12): To a solution of 2-[2-(4-fluorophenyl)acetyl]-4-oxo-pyrazolidine-1-carboxylic acid benzyl ester, **11**, (0.14 g, 0.4 mmol) and morpholine (0.038 mL, 0.43 mmol) in THF at room temperature is added $Na(OAc)_3BH$ (0.125 g, 0.6 mmol) and HOAc (0.022 mL, 0.4 mmol). The solution is stirred 12 hours then partitioned between diethyl ether and $NaHCO_3$. The aqueous layer was extracted several times with ether and the organic layers combined, dried, and concentrated *in vacuo* to a clear oil which was re-dissolved in ether and one equivalent of ethereal HCl is added and a white solid forms. The solid is collected by filtration and 100 mg (60% yield) of the desired product is isolated as the HCl salt.

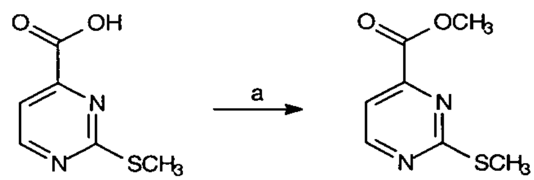
Preparation of 2-(4-Fluorophenyl)-1-(4-morpholin-4-yl-pyrazolidin-1-yl)-ethanone (13): 2-[2-(4-Fluorophenyl)acetyl]-4-morpholin-4-yl-pyrazolidine-1-carboxylic acid benzyl ester HCl salt, **12**, (100 mg, 0.2 mmol) is dissolved in methanol and Pd/C (5 mg) is added. The solution is then hydrogenated in a Parr® Hydrogenation Apparatus for 3 days after which time the catalyst is removed by filtration and the filtrate concentrated *in vacuo* to afford 55 mg (81% yield) of the desired product as a tan solid.

Once the selected 6-amino unit is in position on the 2-R^1-substitued-pyrazolo[1,2-*a*}pyrazol-1-one scaffold, segments of the final analogs which comprise the selected R units can be assembled utilizing a convergent synthetic step. This step makes use of Intermediate Type V compounds having the general formula:



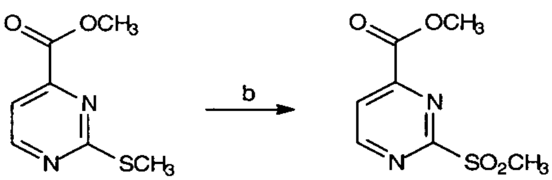
thereby introducing the desired –OR^3 unit into the scaffold, said Type V intermediates can be prepared according to the procedure outlined in the scheme herein below.

General Scheme for Intermediate Type V



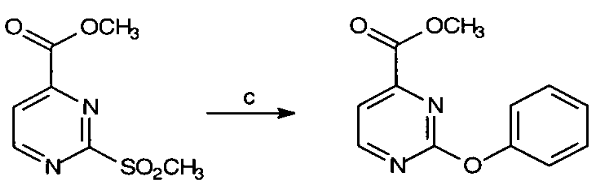
14

Reagents and conditions: (a) $SOCl_2$, MeOH; rt 12 hr.



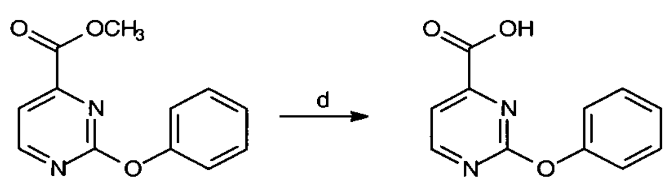
14 **15**

Reagents and conditions: (b) Oxone®, MeOH/THF/H_2O; rt 12 hr.



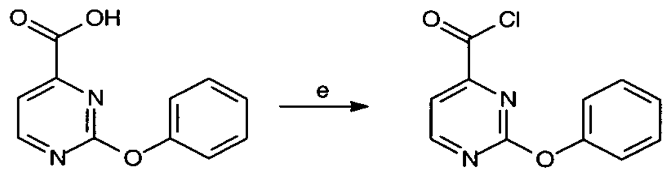
15 **16**

Reagents and conditions: (c) phenol, NaH, THF; rt 12 hr.



16 **17**

Reagents and conditions: (d) NaOH MeOH/H_2O; rt 1.5 hr.



17 18

Reagents and conditions: (e) oxalyl chloride, CH_2Cl_2/DMF; rt 2 hr.

EXAMPLE 7

2-Phenoxy-pyrimidine-4-carbonyl chloride (18)

Preparation of 2-methylsulfanyl-pyrimidine-4-carboxylic acid methyl ester (14): To a suspension of 2-methylsulfanyl-pyrimidine-4-carboxylic acid (15 g, 88 mmol) in methanol (200 mL) is added dropwise thionyl chloride (25 mL). The solution is allowed to warm to room temperature and stir 12 hours. The solution is then concentrated *in vacuo* and the yellow solid which remains can be taken up in methylene chloride and re-concentrated to afford 19 g (97% yield) of the HCl salt of the desired product as a white solid.

Preparation of 2-methanesulfonyl-pyrimidine-4-carboxylic acid methyl ester (15): An aqueous solution (1 L) of Oxone® (211.7 g, 344 mmol) is added dropwise at 0 °C to a solution of 2-methyl-sulfanyl-pyrimidine-4-carboxylic acid methyl ester, **14**, (19 g,86.1 mmol) in 1:1 methanol/THF (1 L). The reaction solution is allowed to warm to room temperature and stir for 1.5 hours. The resulting suspension is partitioned between methylene chloride and water. The aqueous phase is made alkaline with the addition of NaOH and re extracted with solvent. The combined organic layers are dried, filtered, and concentrated *in vacuo* to afford 18.4 g of the desired product as a yellow oil.

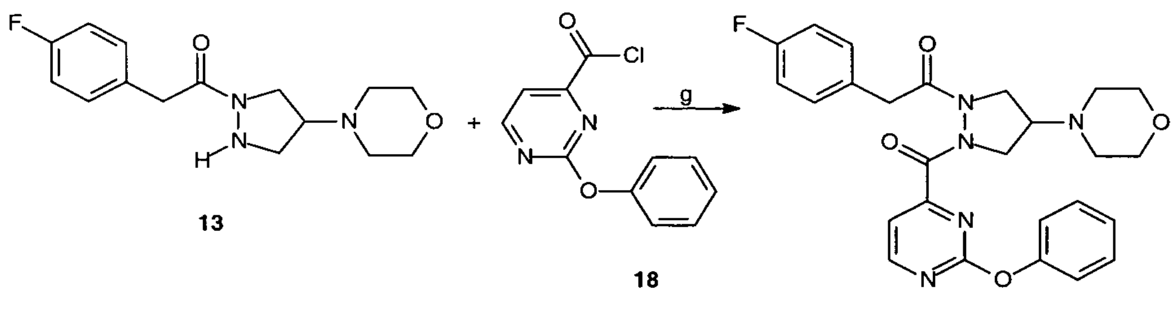
Preparation of 2-phenoxy-pyrimidine-4-carboxylic acid methyl ester (16): NaH (3.5 g of a 60% suspension, 87.4 mmol) is added to a solution of phenol (8.23 g, 87.4 mmol) in THF (100 mL) at room temperature. 2-Methanesulfonyl-pyrimidine-4-carboxylic acid methyl ester, **15**, (6.3 g, 29.1 mmol) is dissolved in THF (60 mL) and added dropwise to the solution of phenol. The reaction is allowed to stir for 12 hours then quenched by the addition of saturated aqueous NH_4Cl. The aqueous phase is extracted with methylene chloride and the combined organic layers are dried, filtered, and concentrated *in vacuo* to afford a crude oil which is purified over silica (ethyl acetate/hexane 2:3) to afford 1.72 g (25% yield) of the desired product as a white solid.

Preparation of 2-phenoxy-pyrimidine-4-carboxylic acid (17): To a solution of 2-phenoxy-pyrimidine-4-carboxylic acid methyl ester, **16**, (1.72 g, 74.8 mmol) in methanol (50 mL) is

added a 50% NaOH solution (10 mL) at room temperature. After stirring for 1.5 hours the solvent is removed *in vacuo* and the remaining aqueous phase is extracted with ethyl acetate. The aqueous phase can then be carefully acidified with concentrated HCl and the white solid which forms extracted twice with ethyl acetate. The organic layers are combined, dried and concentrated *in vacuo* to afford 0.95 g (60% yield) of the desired product as a white solid.

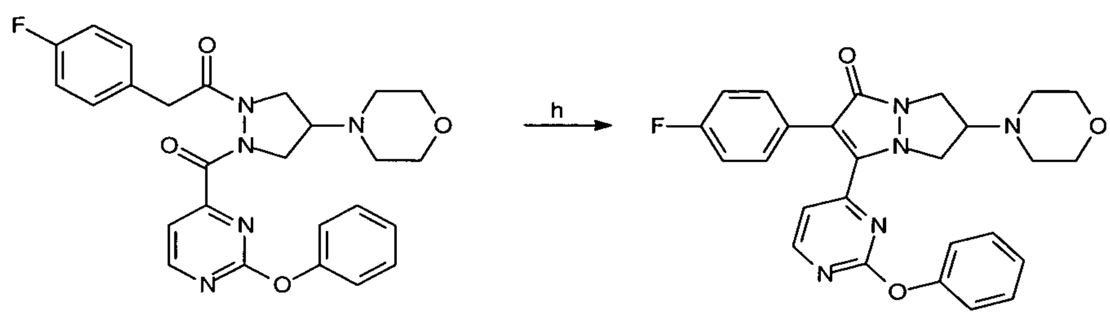
Preparation of 2-phenoxy-pyrimidine-4-carbonyl chloride (18): To a solution of 2-phenoxy-pyrimidine-4-carboxylic acid, **17**, (0.19 g, 0.89 mmol) in methylene chloride (10 mL) containing a few drops of DMF is added oxalyl chloride (0.1 mL). The solution is stirred for 2 hours at room temperature and concentrated *in vacuo* to afford the desired product which is used without further purification.

The final sequence for preparing the compounds which comprise the first aspect of Category II analogs according to the present invention can be accomplished by the procedure outlined herein below. This procedure involves a convergent step wherein the first half comprises the selected R^1 unit and the 6-position amino unit, for example, as intermediate **13**, while the second half comprises the final R unit already introduced to the pyrimidine ring, for example, as in intermediate **18**.



13 **18** **19**

Reagents and Conditions: (g) NaOH: CH_2Cl_2/water, rt 12 hr.



19 **20**

Reagents and Conditions: (h) NaH, DMF; 0 °C, 2 hr.

EXAMPLE 8

2-(4-Fluorophenyl)-6-morpholin-4-yl-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (20)

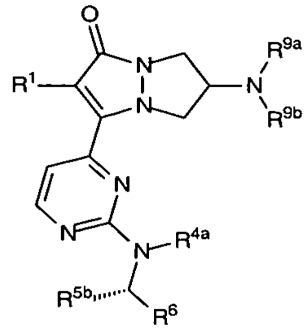
Preparation of 2-(4-fluorophenyl)-1-[4-morpholin-4-yl-2-(2-phenoxy-pyrimidine-4-carbonyl)pyrazolidine-1-yl]ethanone (19): 2-Phenoxypyrimidine-4-carbonyl chloride, **18**, (0.07 g, 0.28 mmol) in methylene chloride (1.5 mL) is added dropwise to a suspension of 2-(4-fluorophenyl)-1-(4-morpholin-4-yl-pyrazolidin-1-yl)ethanone,**13**, (0.06 g, 0.18 mmol) in a 2: 5 water/CH_2Cl_2 solution (7 mL) containing NaOH (0.0112 g, 0.28 mmol) at room temperature. The solution is stirred 18 hours and diluted with additional 2:5 water/CH_2Cl_2. The layers are allowed to separate and the aqueous phase extracted with additional methylene chloride. The organic layers are combined, dried, filtered and concentrated *in vacuo* to afford a tan solid which is purified by preparative HPLC to provide 0.021 g (23% yield) of the desired product as an oily solid.

Preparation of 2-(4-fluorophenyl)-6-morpholin-4-yl-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one (20): To a solution of 2-(4-fluorophenyl)-1-[4-morpholin-4-yl-2-(2-phenoxy-pyrimidine-4-carbonyl)pyrazolidine-1-yl]ethanone, **19**, (0.2 g, 0.4 mmol) in DMF (10 mL) at 0 °C is added NaH (0.024 g, 0.6 mmol) and the resulting solution is stirred 2 hours. The solvent is removed *in vacuo* the residue dissolved in methylene chloride and extracted with water, dried, and re-concentrated to afford 37 mg (20% yield) of the desired product as a yellow solid.

The following compounds from the first aspect of Category II can be prepared by the procedure described herein above.

2-(4-Fluorophenyl)-6-morpholin-4-yl-3-[2-(4-flurorophenoxy)-pyrimidin-4-yl]-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one: ^1H NMR ($CDCl_3$, 300 MHz) δ1.61 (s, 4H), 2.58 (s, 4H), 3.70-3.99 (m, 4H), 4.23-4.25 (m, 1H), 6.94 (d, 1H, *J*= 5.1 Hz), 7.10 (t, 2H, *J*= 8.7 Hz), 7.26-7.41 (m, 6H), 8.50 (d, 1H, *J*= 5.1 Hz). ESI^+ MS: m/z (rel intensity) 491.9 (100, M^++H). Anal. Calculated for $C_{26}H_{23}F_2N_5O_3$ $0.5H_2O$: C, 62.39; H, 4.83; N, 13.99. Found: C, 62.02; H, 4.38; N, 13.62.

The second aspect of Category II analogs relates to compounds having the formula:



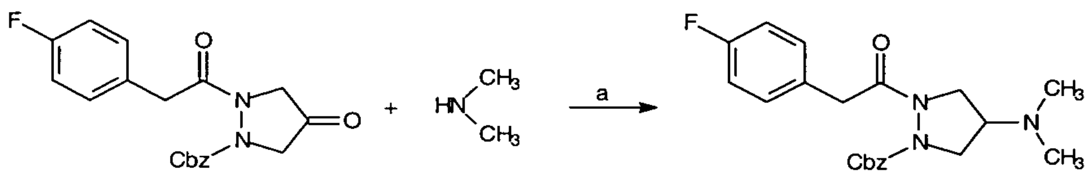
wherein R is an amino unit as indicated in the formula. The analogs of Table IV comprise R units having the formula $-NHC(HR^{5b})R^{6}$ wherein R^{4a} is hydrogen and R^{1}, R^{5a}, R^{6}, R^{9a}, and R^{9b} are described herein.

TABLE IV

No.	R^1	R^{5b}	R^6	R^{9a}	R^{9b}
173	4-fluorophenyl	H	phenyl	H	H
174	4-fluorophenyl	H	4-fluorophenyl	H	H
175	4-fluorophenyl	H	2-aminophenyl	H	H
176	4-fluorophenyl	H	2-methylphenyl	H	H
177	4-fluorophenyl	H	4-methylphenyl	H	H
178	4-fluorophenyl	H	4-methoxyphenyl	H	H
179	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	H	H
180	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	H	H
181	4-fluorophenyl	H	pyridin-2-yl	H	H
182	4-fluorophenyl	H	pyridin-3-yl	H	H
183	4-fluorophenyl	methyl	phenyl	H	H
184	4-fluorophenyl	methyl	4-fluorophenyl	H	H
185	4-fluorophenyl	methyl	2-aminophenyl	H	H
186	4-fluorophenyl	methyl	2-methylphenyl	H	H
187	4-fluorophenyl	methyl	4-methylphenyl	H	H
188	4-fluorophenyl	methyl	4-methoxyphenyl	H	H
189	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	H	H
190	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	H	H
191	4-fluorophenyl	methyl	pyridin-2-yl	H	H
192	4-fluorophenyl	methyl	pyridin-3-yl	H	H
193	4-fluorophenyl	H	phenyl	methyl	methyl
194	4-fluorophenyl	H	4-fluorophenyl	methyl	methyl
195	4-fluorophenyl	H	2-aminophenyl	methyl	methyl

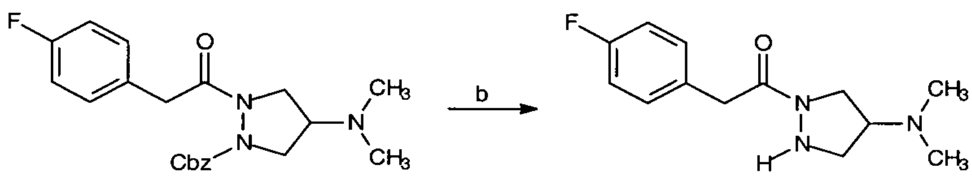
196	4-fluorophenyl	H	2-methylphenyl	methyl	methyl
197	4-fluorophenyl	H	4-methylphenyl	methyl	methyl
198	4-fluorophenyl	H	4-methoxyphenyl	methyl	methyl
199	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	methyl	methyl
200	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	methyl	methyl
201	4-fluorophenyl	H	pyridin-2-yl	methyl	methyl
202	4-fluorophenyl	H	pyridin-3-yl	methyl	methyl
203	4-fluorophenyl	methyl	phenyl	methyl	methyl
204	4-fluorophenyl	methyl	4-fluorophenyl	methyl	methyl
205	4-fluorophenyl	methyl	2-aminophenyl	methyl	methyl
206	4-fluorophenyl	methyl	2-methylphenyl	methyl	methyl
207	4-fluorophenyl	methyl	4-methylphenyl	methyl	methyl
208	4-fluorophenyl	methyl	4-methoxyphenyl	methyl	methyl
209	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	methyl	methyl
210	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	methyl	methyl
211	4-fluorophenyl	methyl	pyridin-2-yl	methyl	methyl
212	4-fluorophenyl	methyl	pyridin-3-yl	methyl	methyl
213	4-fluorophenyl	$-CO_2CH_3$	phenyl	H	H
214	4-fluorophenyl	$-CO_2CH_3$	4-fluorophenyl	H	H
215	4-fluorophenyl	$-CO_2CH_3$	2-aminophenyl	H	H
216	4-fluorophenyl	$-CO_2CH_3$	2-methylphenyl	H	H
217	4-fluorophenyl	$-CO_2CH_3$	4-methylphenyl	H	H
218	4-fluorophenyl	$-CO_2CH_3$	4-methoxyphenyl	H	H
219	4-fluorophenyl	$-CO_2CH_3$	4-(propanesulfonyl)phenyl	H	H
220	4-fluorophenyl	$-CO_2CH_3$	3-benzo[1,3]dioxol-5-yl	H	H
221	4-fluorophenyl	$-CO_2CH_3$	pyridin-2-yl	H	H
222	4-fluorophenyl	$-CO_2CH_3$	pyridin-3-yl	H	H
223	4-fluorophenyl	$-CO_2CH_3$	phenyl	methyl	methyl
224	4-fluorophenyl	$-CO_2CH_3$	4-fluorophenyl	methyl	methyl
225	4-fluorophenyl	$-CO_2CH_3$	2-aminophenyl	methyl	methyl
226	4-fluorophenyl	$-CO_2CH_3$	2-methylphenyl	methyl	methyl
227	4-fluorophenyl	$-CO_2CH_3$	4-methylphenyl	methyl	methyl
228	4-fluorophenyl	$-CO_2CH_3$	4-methoxyphenyl	methyl	methyl
229	4-fluorophenyl	$-CO_2CH_3$	4-(propanesulfonyl)phenyl	methyl	methyl
230	4-fluorophenyl	$-CO_2CH_3$	3-benzo[1,3]dioxol-5-yl	methyl	methyl
231	4-fluorophenyl	$-CO_2CH_3$	pyridin-2-yl	methyl	methyl
232	4-fluorophenyl	$-CO_2CH_3$	pyridin-3-yl	methyl	methyl

The compounds which comprise the second aspect of Category II analogs wherein R is an amino unit, can be prepared by the Scheme outlined herein below starting with common intermediate **11**. For the following example R^{9a} and R^{9b} are each methyl and R is (*S*)-(1-phenyl)ethylamino.



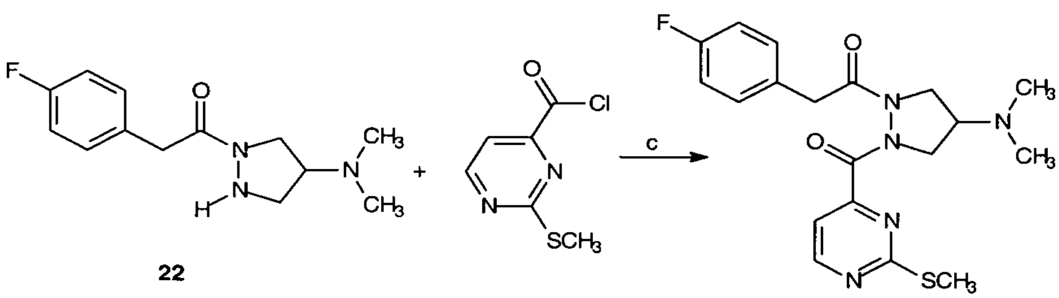
11 **21**

Reagents and Conditions: (a) $Na(OAc)_3BH$, HOAc, THF; rt 12 hr.



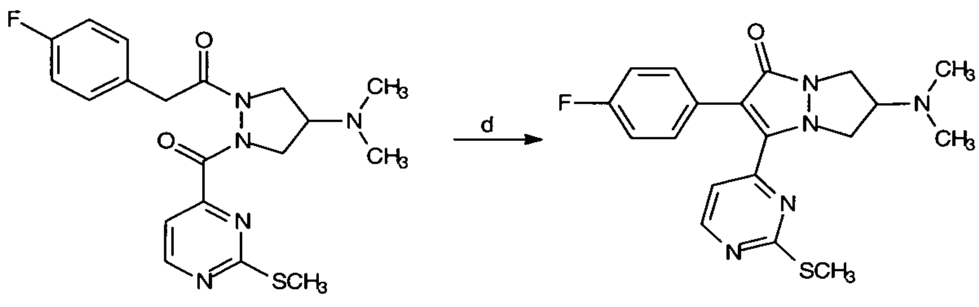
21 **22**

Reagents and Conditions: (b) H_2; Pd/C, MeOH.



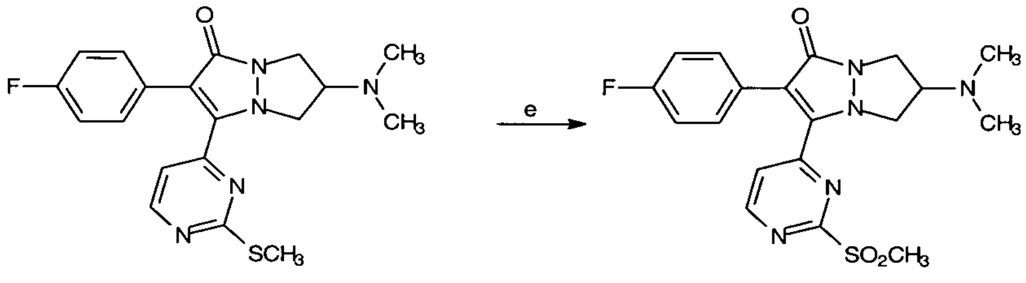
22 **23**

Reagents and Conditions: (c) NaOH: CH_2Cl_2/water, rt 12 hr.



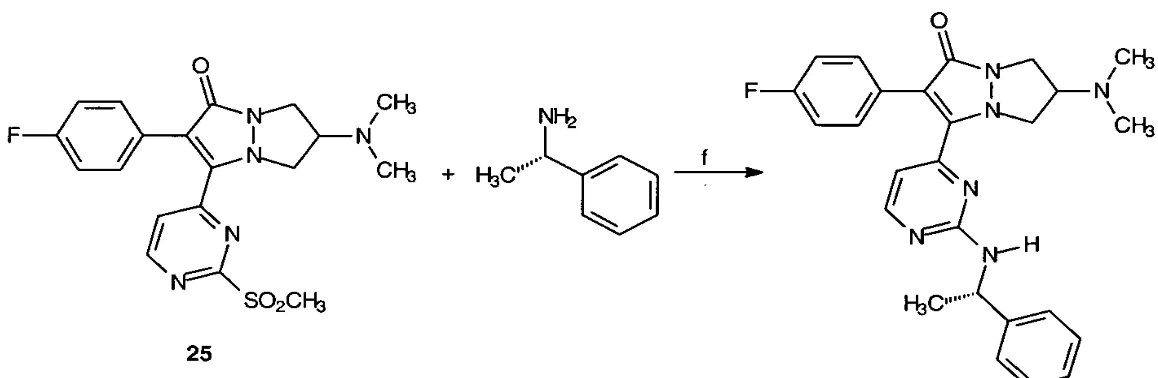
23 24

Reagents and Conditions: (d) NaH, DMF; 0 °C to rt, 2 hr.



24 25

Reagents and Conditions: (e) Oxone®, MeOH/THF/H_2O; rt 12 hr.



25 26

Reagents and Conditions: (f) toluene, 140 °C, 12 hr.

EXAMPLE 9

6-Dimethylamino-2-(4-fluorophenyl)-3-[2-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (26)

Preparation of 4-dimethylamino-2-[2-(4-fluorophenyl)acetyl]-pyrazolidine-1-carboxylic acid benzyl ester (21): To a solution of 2-[2-(4-fluorophenyl)acetyl]-4-oxo-pyrazolidine-1-carboxylic acid benzyl ester, **11**, (3.6 g, 10 mmol) and dimethylamine (10 mL of a

2M solution, 20 mmol) in THF at room temperature is added $Na(OAc)_3BH$ (3.1 g, 15 mmol) and HOAc (0.6 g, 10 mmol). The solution is stirred 12 hours then partitioned between diethyl ether and $NaHCO_3$. The aqueous layer was extracted several times with ether and the organic layers combined, dried, and concentrated *in vacuo* to a clear oil which was re-dissolved in ether and one equivalent of ethereal HCl is added and a white solid forms. The solid is collected by filtration to afford the desired product as the HCl salt.

Preparation of 1-(4-dimethylamino-pyrazolidin-1-yl)-2-(4-fluorophenyl)-ethanone (22): 4-dimethylamino-2-[2-(4-fluorophenyl)acetyl]-pyrazolidine-1-carboxylic acid benzyl ester HCl salt, **21**, (4.22 g, 10 mmol) is dissolved in methanol and Pd/C (100 mg) is added. The solution is then hydrogenated of a Parr® Hydrogenation Apparatus 18 hours after which time the catalyst is removed by filtration and the filtrate concentrated *in vacuo* to afford the desired product.

Preparation of 1-[4-dimethylamino-2-(2-methylsulfanyl-pyrimidine-4-carbonyl)-pyrazolidin-1-yl]-2-(4-fluorophenyl)-ethanone (23): To a solution of 1-(4-dimethylamino-pyrazolidin-1-yl)-2-(4-fluorophenyl)-ethanone, **22**, (2.5 g, 10 mmol) in dichloromethane (20 mL) is added 2-methylsulfonyl-pyrimidine-4-carbonyl chloride (3.7 g, 20 mmol) followed by dropwise addition of a 1.0 N aqueous solution of sodium hydroxide (35 mL). The mixture is vigorously stirred at room temperature for 12 hours. The reaction is diluted with dichloromethane (100 mL) and washed with water (100 mL). The aqueous layer is back-extracted with dichloromethane (100 mL). The combined organic layers are washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried, filtered and concentrated *in vacuo*. The resulting crude material is purified over silica (1:1 hexane/ethyl acetate to 100% ethyl acetate) to afford the desired product.

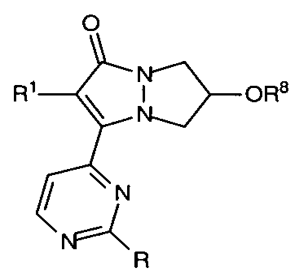
Preparation of 6-dimethylamino-2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (24): 1-[4-Dimethylamino-2-(2-methylsulfanyl-pyrimidine-4-carbonyl)-pyrazolidin-1-yl]-2-(4-fluorophenyl)-ethanone, **23,** (4.0 g, 10 mmol) is dissolved in THF (75 mL). This solution is then added dropwise *via* cannula to a suspension of NaH (0.440 g of a 60% dispersion in mineral oil, 11 mmol) at –30 °C. The reaction is allowed to gradually warm to 0 °C over 3 hours. The reaction is quenched with NH_4Cl (sat. aq.) (15 mL). The mixture is stirred at room temperature, then concentrated *in vacuo*. The residue is diluted with tetrahydrofuran (250 mL) and the mixture filtered through Celite. The filtrate is concentrated *in vacuo* to give an oil. The crude product is purified over silica (100% ethyl acetate to 5% to 10% to 20% methyl alcohol/ethyl acetate) to afford the desired product.

Preparation of 6-dimethylamino-2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (25): To a solution of 6-dimethylamino-2-(4-

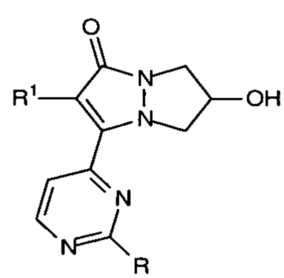
fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, **24**, (3.9 g, 10 mmol) in THF:methanol (150 mL of a 1:1 mixture) is added dropwise a solution of Oxone® (potassium peroxymonosulfate) (24.3 g, 39.5 mmol) in water (100 mL). The reaction is stirred 1 hour at room temperature, diluted with aqueous $NaHCO_3$ and extract three times with ethyl acetate. The organic layers are combined, dried, and concentrated *in vacuo* to afford the crude desired product which is used without further purification.

Preparation of 6-dimethylamino-2-(4-fluorophenyl)-3-[2-(1-(*S*)-phenylethylamino)-pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (26): A solution of the crude 6-dimethylamino-2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, **25**, prepared as described herein above (4.2 g, 10 mmol) and (*S*)-(-)-α-methyl-benzyl amine (45.2 mL, 351 mmol) are dissolved in toluene (100 mL). The resulting mixture is heated to 140 °C for 12 hours, cooled to room temperature and the solvent removed *in vacuo*. The resulting residue is purified over silica (1:1 EtOAc/hexanes) to afford the desired product.

Category III of inflammatory cytokine release inhibiting compounds according to the present invention have the general scaffold having the formula:



the first aspect of which relates to ether analogs having the formula:



wherein R and R^1 units are defined herein below in Table IV.

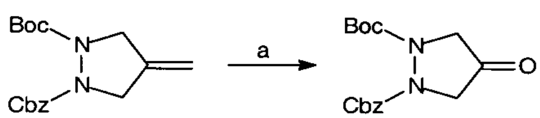
TABLE IV

No.	R^1	R

233	4-fluorophenyl	phenoxy
234	4-fluorophenyl	2-fluorophenoxy
235	4-fluorophenyl	3-fluorophenoxy
236	4-fluorophenyl	4-fluorophenoxy
237	4-fluorophenyl	2,6-difluorophenoxy
238	4-fluorophenyl	2-cyanophenoxy
239	4-fluorophenyl	3-cyanophenoxy
240	4-fluorophenyl	2-trifluoromethylphenoxy
241	4-fluorophenyl	4-trifluoromethylphenoxy
242	4-fluorophenyl	2-methylphenoxy
243	4-fluorophenyl	4-methylphenoxy
244	4-fluorophenyl	2,4-dimethylphenoxy
245	4-fluorophenyl	3-N-acetylaminophenoxy
246	4-fluorophenyl	2-methoxyphenoxy
247	4-fluorophenyl	4-methoxyphenoxy
248	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
249	3-fluorophenyl	phenoxy
250	3-fluorophenyl	2-fluorophenoxy
251	3-fluorophenyl	3-fluorophenoxy
252	3-fluorophenyl	4-fluorophenoxy
253	3-fluorophenyl	2,6-difluorophenoxy
254	3-fluorophenyl	2-cyanophenoxy
255	3-fluorophenyl	3-cyanophenoxy
256	3-fluorophenyl	2-trifluoromethylphenoxy
257	3-fluorophenyl	4-trifluoromethylphenoxy
258	3-fluorophenyl	2-methylphenoxy
259	3-fluorophenyl	4-methylphenoxy
260	3-fluorophenyl	2,4-dimethylphenoxy
261	3-fluorophenyl	3-N-acetylaminophenoxy
262	3-fluorophenyl	2-methoxyphenoxy
263	3-fluorophenyl	4-methoxyphenoxy
264	3-fluorophenyl	3-benzo[1,3]dioxol-5-yl
265	3-trifluoromethylphenyl	phenoxy
266	3-trifluoromethylphenyl	2-fluorophenoxy
267	3-trifluoromethylphenyl	3-fluorophenoxy
268	3-trifluoromethylphenyl	4-fluorophenoxy
269	3-trifluoromethylphenyl	2,6-difluorophenoxy

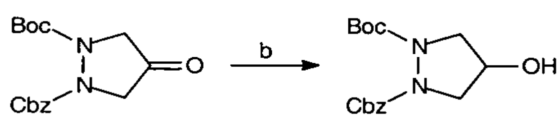
270	3-trifluoromethylphenyl	2-cyanophenoxy
271	3-trifluoromethylphenyl	3-cyanophenoxy
272	3-trifluoromethylphenyl	2-trifluoromethylphenoxy
273	3-trifluoromethylphenyl	4-trifluoromethylphenoxy
274	3-trifluoromethylphenyl	2-methylphenoxy
275	3-trifluoromethylphenyl	4-methylphenoxy
276	3-trifluoromethylphenyl	2,4-dimethylphenoxy
277	3-trifluoromethylphenyl	3-N-acetylaminophenoxy
278	3-trifluoromethylphenyl	2-methoxyphenoxy
279	3-trifluoromethylphenyl	4-methoxyphenoxy
280	3-trifluoromethylphenyl	3-benzo[1,3]dioxol-5-yl

The compounds which comprise the first aspect of the Category III compounds can be prepared by the scheme outline below utilizing intermediate **8** as a convenient starting material.



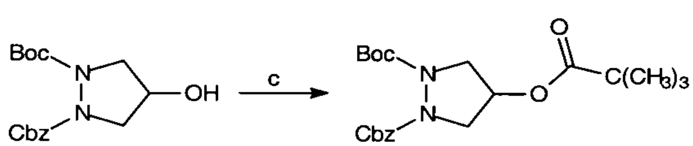
8 **27**

Reagents and conditions: (a) O_3, CH_2Cl_2, THF; -78 °C 20 min., rt 12 hr.



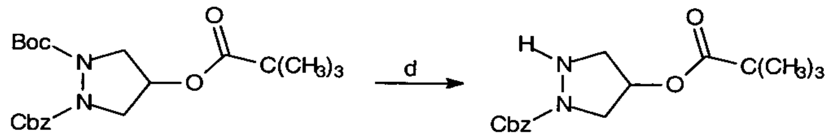
27 **28**

Reagents and conditions: (b) BH_3:DMS, THF; -78 °C 40 min.



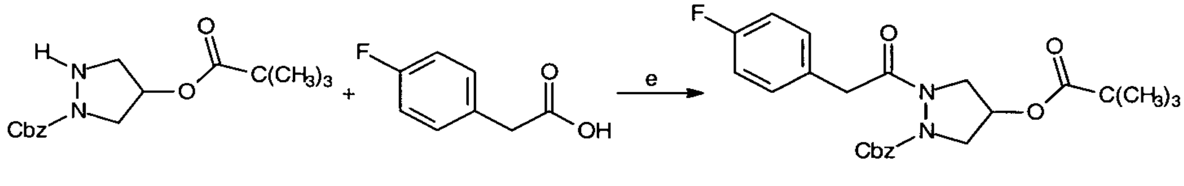
28 **29**

Reagents and conditions: (c) $(CH_3)_3CCOCl$, pyridine, DMAP; rt 12 hr.



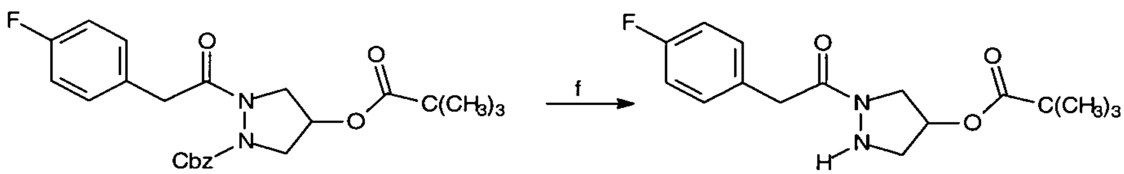
29 30

Reagents and conditions: (d) $SOCl_2$, MeOH; 0 °C to rt, 12 hr.



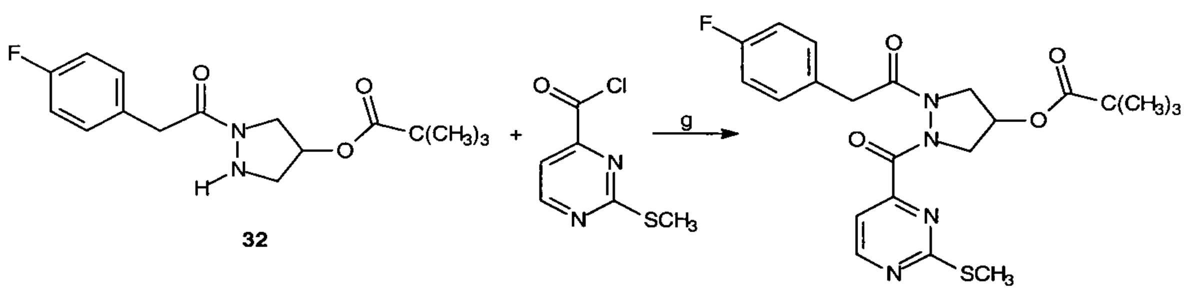
30 31

Reagents and conditions: (e) Et_3N at 0 °C; RCO_2H at rt; EDCI, CH_2Cl_2; 0 °C to rt, 12 hr.



31 32

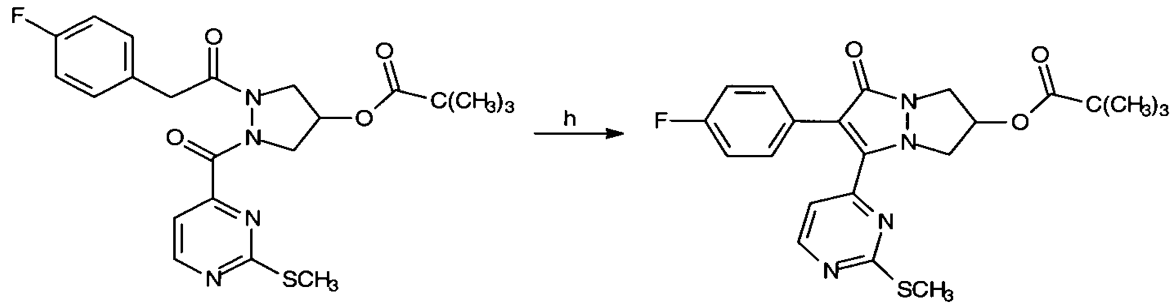
Reagents and conditions: (f) H_2: Pd/C, MeOH; rt 6 hr.



32

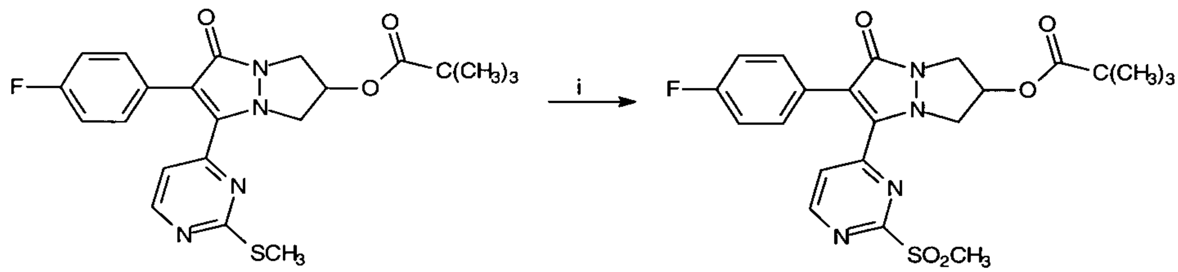
33

Reagents and Conditions: (g) NaOH: CH_2Cl_2/water, rt 12 hr.



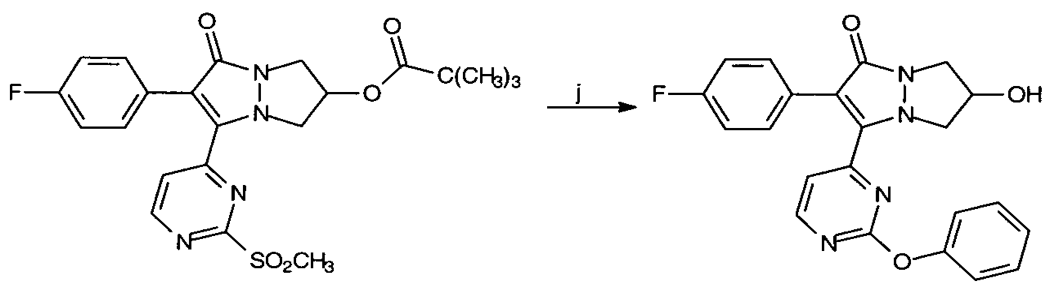
33 34

Reagents and Conditions: (h) NaH, DMF; 0 °C to rt, 3 hr.



34 35

Reagents and Conditions: (i) Oxone®, MeOH/THF/H_2O; rt 12 hr.



35 36

Reagents and Conditions: (j) phenol, base,0 °C to rt 1 hr.

EXAMPLE 10

2-(4-Fluorophenyl)-6-hydroxy-3-(2-phenoxypyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (36)

Preparation of 4-oxo-pyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (27): 4-methylene-pyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **8**, (23.9 g, 75.1 mmol) is dissolved in dichloromethane (200 mL). The solution is cooled to –78 °C and purged with oxygen for 5 minutes. Ozone gas is passed through the solution until a deep blue color persists in the solution (approx. 20 minutes). The solution is purged with oxygen and argon,

and then charged with 40 mL of dimethylsulfide. The cooling bath is removed, and the solution stirred at ambient temperature for 12 hours. The reaction solution is then concentrated *in vacuo* and the resulting oil purified over silica (3:1 to 2:1 hexane/ethyl acetate) to afford 13.5 g (56% yield).of the desired product as a viscous, clear oil

Preparation of 4-hydroxypyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (28): 4-Oxo-pyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **27**, (5.0 g, 15.6 mmol) is dissolved in tetrahydrofuran (150 mL) and the solution cooled to –78 °C. A 5.0 M solution of borane-dimethyl sulfide complex in ether (6.24 mL, 31.2 mmol) is added dropwise *via* syringe. After 40 minutes at –78 °C, the reaction is quenched by slow addition of a saturated aqueous solution of ammonium chloride (20 mL). The cooling bath is removed, and the mixture allowed to warm to ambient temperature with vigorous stirring. The solvent is removed *in vacuo* and the residue diluted with dichloromethane (200 mL). The mixture is washed with water (150 mL) and saturated aqueous sodium bicarbonate solution (150 mL), water and brine. The combined aqueous layers are extracted with dichloromethane (200 mL), water (150 mL), NaCl (sat.) (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 4.66 g (93% yield) of the desired product as a clear, viscous oil.

Preparation of 4-(2,2-dimethylpropionyloxy)pyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (29): 4-Hydroxypyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **28**, (1.42 mg, 4.40 mmol) is dissolved in pyridine (22 mL). 4-Dimethylamino-pyridine (10 mg) is added followed by trimethylacetyl chloride (1.63 mL, 13.2 mmol). The reaction is stirred at ambient temperature for 12 hours. The cloudy reaction mixture is then concentrated *in vacuo* to afford a white residue. Dichloro-methane (75 mL) is added to the residue and the mixture washed with a 1.0 N aqueous solution of hydrochloric acid (75 mL). The aqueous layer is extracted with dichloro-methane (75 mL), the combined organic layers washed with a saturated aqueous solution of $NaHCO_3$ (75 mL), water (75 mL), brine (75 mL), then dried, filtered and concentrated *in vacuo* to afford the crude product. The crude product is purified over silica(4:1 to 1:1 hexane/ethyl acetate) to afford 1.76 g (98% yield) of the desired product as a clear, viscous oil.

Preparation of 4-(2,2-dimethylpropionyloxy)pyrazolidine-1-carboxylic acid 1-benzyl ester (30): 4-(2,2-Dimethylpropionyloxy)pyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **29**, (1.76 g, 4.33 mmol) is dissolved in methanol (40 mL) and the solution cooled to 0 °C. Thionyl chloride (3.16 mL, 43.3 mmol) is added dropwise and the reaction allowed to warm to room temperature and continue stirring 12 hours. The reaction solution is concentrated *in vacuo* to give afford 1.45 g (98% yield) of the desired product as the HCl salt as an off-white solid.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-(2,2-dimethylpropionyloxy)-pyrazolidine-1-carboxylic acid 1-benzyl ester (31): 4-(2,2-Dimethylpropionyloxy)-pyrazolidine-1-carboxylic acid 1-benzyl ester, **30**,(1.45 g, 4.23 mmol) is dissolved in dichloromethane (21 mL). The solution is cooled to 0 °C and triethylamine (1.30 mL, 9.31 mmol) added dropwise via syringe. The cold bath is removed and the reaction allowed to warm to room temperature and continue stirring 20 minutes. 4-Fluorophenylacetic acid (848 mg, 5.50 mmol) is added. After stirring for 5 minutes, the reaction mixture is transferred via cannula into a solution of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrogen chloride in dichloromethane (21 mL) maintained at 0 °C. The reaction is allowed to stir and gradually warm to room temperature over 12 hours. The reaction is washed with a 5% aqueous solution of Na_2CO_3 (2 X 50 mL). The combined aqueous layers are extracted several times with dichloromethane (50 mL) and the combined organic layers washed with brine, dried, filtered and concentrated *in vacuo*. The crude product is purified over silica (2:1 to 1:1 hexane/ethyl acetate) to afford 1.71 g (91% yield) of the desired product as a white solid.

Preparation of 2,2-dimethyl-propionic acid 1-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester (32): 2-[2-(4-Fluorophenyl)acetyl]-4-(2,2-dimethylpropionyloxy)-pyrazolidine-1-carboxylic acid 1-benzyl ester, **31**, (1.71 g, 3.86 mmol) is dissolved in methanol (40 mL). The flask is flushed with nitrogen and charged with 10% palladium on carbon (300 mg). The reaction flask is stirred vigorously at room temperature under 1 atmosphere of hydrogen gas for 6 hours. The flask is flushed with nitrogen and the reaction mixture filtered through a pad of Celite, rinsing with ethyl acetate (100 mL). The filtrate is concentrated *in vacuo* to afford 1.18 g (98% yield) of the desired product as a tan solid.

Preparation of 2,2-dimethyl-propionic acid 1-[2-(4-fluorophenyl)acetyl]-2-(methylsulfanyl-pyrimidine-4-carbonyl)-pyrazolidin-4-yl ester (33): To a solution of 2,2-dimethyl-propionic acid 1-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester, **32**, (427 mg, 1.79 mmol) in dichloromethane (3 mL) is added 2-methylsulfonyl-pyrimidine-4-carbonyl chloride (676 mg, 3.58 mmol) followed by dropwise addition of a 1.0 N aqueous solution of sodium hydroxide (6 mL). The mixture is vigorously stirred at room temperature for 12 hours. The reaction is diluted with dichloromethane (25 mL) and washed with water (25 mL). The aqueous layer is back-extracted with dichloromethane (25 mL). The combined organic layers are washed with a saturated aqueous solution of sodium bicarbonate (25 mL) and brine (25 mL), dried, filtered and concentrated *in vacuo*. The resulting crude material is purified over silica (1:1 hexane/ethyl acetate to 100% ethyl acetate) to afford 464 mg (96.6% yield) of the desired product as a brown, viscous oil.

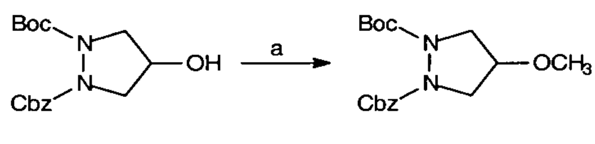
Preparation of 2,2-dimethyl-propionic acid 6-(4-fluorophenyl)-7-(2-methylsulfanyl-pyrimidin-4-yl)-5-oxo-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl ester (34): 2,2-Dimethyl-propionic acid 1-[2-(4-fluorophenyl)acetyl]-2-(methylsulfanyl-pyrimidine-4-carbonyl)-pyrazolidin-4-yl ester, **33**, (300 mg, 0.651 mmol) is dissolved in THF (6 mL). This solution is then added dropwise *via* cannula to a suspension of NaH (29 mg of a 60% dispersion in mineral oil, 0.716 mmol) at –30 °C. The reaction is allowed to gradually warm to 0 °C over 3 hours. The reaction is quenched with NH_4Cl (sat. aq.) (1 mL). The mixture is stirred at room temperature, then concentrated *in vacuo*. The residue is diluted with tetrahydrofuran (50 mL) and the mixture filtered through Celite. The filtrate is concentrated *in vacuo* to give an orange oil. The crude product is purified over silica (100% ethyl acetate to 5% to 10% to 20% methyl alcohol/ethyl acetate) to afford 87 mg (30% yield) of the desired product as a yellow solid.

Preparation of 2,2-dimethyl-propionic acid 6-(4-fluorophenyl)-7-(2-methane-sulfonyl-pyrimidin-4-yl)-5-oxo-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl ester (35): 2,2-Dimethyl-propionic acid 6-(4-fluorophenyl)-7-(2-methylsulfanyl-pyrimidin-4-yl)-5-oxo-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl ester, **34**, (96 mg, 0.217 mmol) is dissolved in chloroform (2 mL). The solution was cooled to 0 °C and a solution of 3-chloroperbenzoic acid (117 mg of ~77% purity, 0.521 mmol) in chloroform (3 mL) is added dropwise to the yellow suspension. The reaction is stirred at 0 °C for 3 hours, then at room temperature for 12 hours. The yellow-colored reaction solution is washed with $NaHSO_3$ (sat. aq.) (2 X 15 mL). The layers are separated and the aqueous layer extracted with chloroform (2 X 15 mL). The combined organic layers are washed with $NaHCO_3$ (sat. aq.) (20 mL), dried, filtered and concentrated *in vacuo* to afford 50 mg (48% yield) of the desired product as a yellow oil.

Preparation of 2-(4-fluorophenyl)-6-hydroxy-3-(2-phenoxypyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (36): A solution of 2,2-dimethyl-propionic acid 6-(4-fluorophenyl)-7-(2-methane-sulfonyl-pyrimidin-4-yl)-5-oxo-2,3-dihydro-1H,5H-pyrazolo[1,2-a]pyrazol-2-yl ester, **35**, (50 mg, 0.105 mmol) in THF (1 mL) is slowly cannulated into a solution of sodium phenolate in THF (1 mL) at 0 °C. The cooling bath is removed and the reaction stirred at room temperature for 1 hour. The reaction is quenched with NH_4Cl (sat. aq.) (500 µL). The reaction mixture is concentrated *in vacuo* and the residue diluted taken up in ethyl acetate (15 mL). The solution is washed with water (20 mL) and a 5% aqueous Na_2CO_3 (20 mL). The combined aqueous layers are extracted with ethyl acetate (25 mL) and brine (20 mL), dried, filtered and concentrated *in vacuo*. The crude material is purified over silica (100% ethyl acetate to 5% to 10% to 20% methyl alcohol/ethyl acetate) to afford 9 mg (21% yield) of the desired product as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 5.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.31–7.27 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 6.80 (d, J = 5.2 Hz,

1H), 5.41 (br s, 1H), 4.82 (m, 1H), 4.23 (d, *J* = 12.4 Hz, 1H), 3.95–3.85 (m, 2H), 3.76 (dd, *J* = 12.4, 4.4 Hz, 1H); HRMS *m/z* calcd for $C_{22}H_{18}FN_4O_3$ (MH^+) 405.1363, found 405.1365.

This procedure can be used to prepare Category III analogs of the first aspect wherein R^8 is C_1-C_4 alkyl. Conversion of intermediate **28** to an Intermediate of Type IV, for example, the methoxy analog **37**, by the following procedure allows the formulator to assemble 6-alkoxy ring analogs of Category III.



28 **37**

Reagents and conditions: CH_3I, Ag_2O; DMF; dark, rt 12 hr.

EXAMPLE 11

Preparation of 4-methoxypyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester (37): 4-Methoxypyrazolidine-1,2-dicarboxylic acid 1-benzyl ester 2-*tert*-butyl ester, **28**, (2.55 g, 7.91 mmol) is dissolved in dimethylformamide (40 mL). Methyl iodide (1.97 mL, 31.6 mmol) is added followed by silver oxide (3.67 g, 15.8 mmol). The flask is cover with foil and stirred for 12 hours in the absence of light. The reaction mixture is poured into ether (150 mL). The mixture is stirred vigorously at room temperature and filtered through a pad of Celite. The filtrate is washed with water (2 X 150 mL) and brine (150 mL), dried, filtered and concentrated *in vacuo* to afford 2.58 g (97% yield) of the desired product as a yellow, clear oil.

The second aspect of Category III analogs relates to scaffolds having the R^2 substituent at the 6-position of the pyrazolo[1,2-*a*]pyrazol-1-one ring system comprise a carbonyl unit selected from the group consisting of $-(CH_2)_jCO_2R^{10}$; $-(CH_2)_jOCO_2R^{10}$; $-(CH_2)_jCON(R^{10})_2$; and $-(CH_2)_jOCON(R^{10})_2$, wherein R^{10} is the same as defined herein above. A non-limiting example of an analog according to the second aspect of Category III has the formula:

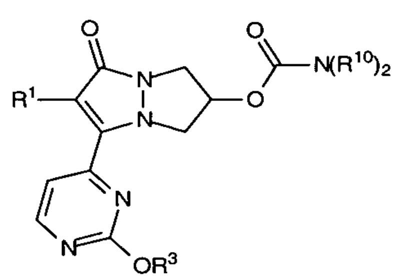


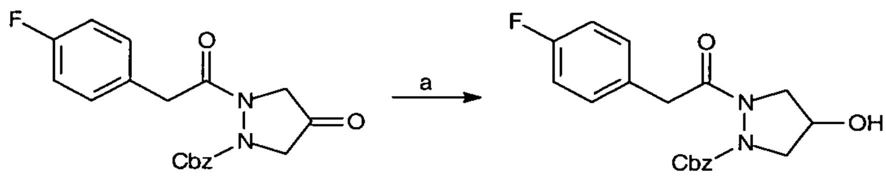
Table VII illustrates examples of this aspect of the present invention wherein two R^{10} units are taken together to form a ring.

TABLE VII

No.	R^1	R^3	R^{10} ring
281	4-fluorophenyl	phenyl	morpholin-1-yl
282	4-fluorophenyl	4-fluorophenyl	morpholin-1-yl
283	4-fluorophenyl	2-aminophenyl	morpholin-1-yl
284	4-fluorophenyl	2-methylphenyl	morpholin-1-yl
285	4-fluorophenyl	4-methylphenyl	morpholin-1-yl
286	4-fluorophenyl	4-methoxyphenyl	morpholin-1-yl
287	4-fluorophenyl	4-(propanesulfonyl)phenyl	morpholin-1-yl
288	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	morpholin-1-yl
289	4-fluorophenyl	pyridin-2-yl	morpholin-1-yl
290	4-fluorophenyl	pyridin-3-yl	morpholin-1-yl
291	4-fluorophenyl	phenyl	piperidin-1-yl
292	4-fluorophenyl	4-fluorophenyl	piperidin-1-yl
293	4-fluorophenyl	2-aminophenyl	piperidin-1-yl
294	4-fluorophenyl	2-methylphenyl	piperidin-1-yl
295	4-fluorophenyl	4-methylphenyl	piperidin-1-yl
296	4-fluorophenyl	4-methoxyphenyl	piperidin-1-yl
297	4-fluorophenyl	4-(propanesulfonyl)phenyl	piperidin-1-yl
298	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	piperidin-1-yl
299	4-fluorophenyl	pyridin-2-yl	piperidin-1-yl
300	4-fluorophenyl	pyridin-3-yl	piperidin-1-yl
301	4-fluorophenyl	phenyl	piperazin-1-yl
302	4-fluorophenyl	4-fluorophenyl	piperazin-1-yl
303	4-fluorophenyl	2-aminophenyl	piperazin-1-yl
304	4-fluorophenyl	2-methylphenyl	piperazin-1-yl
305	4-fluorophenyl	4-methylphenyl	piperazin-1-yl
306	4-fluorophenyl	4-methoxyphenyl	piperazin-1-yl
307	4-fluorophenyl	4-(propanesulfonyl)phenyl	piperazin-1-yl
308	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	piperazin-1-yl
309	4-fluorophenyl	pyridin-2-yl	piperazin-1-yl
310	4-fluorophenyl	pyridin-3-yl	piperazin-1-yl

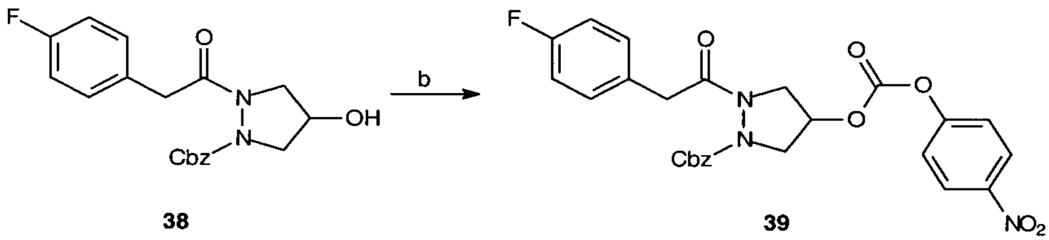
As described herein above, the procedure for preparing compounds included within the first aspect of Category III encompasses a final step wherein the O-protecting unit, *inter alia*, –C(O)C(CH_3)$_3$ is removed during the same step which adds the –OR^3 unit to the scaffold, for example, the conversion of **35** to **36**. For the analogs of the second aspect the following procedure, as outlined below, is use to prepare the analogs wherein one of the 6-position R^2 unit is a carbonyl unit as described herein under the second aspect of Category III.

The following scheme begins with intermediate **11** prepared as described herein above.



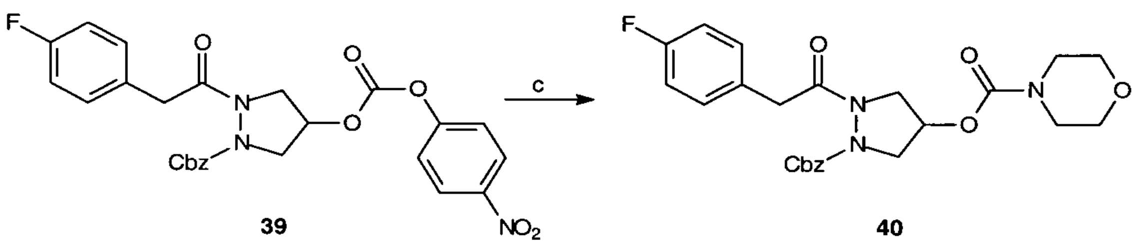
11 **38**

Reagents and conditions: (a) BH_3:DMS, THF; -78 °C 1 hr.



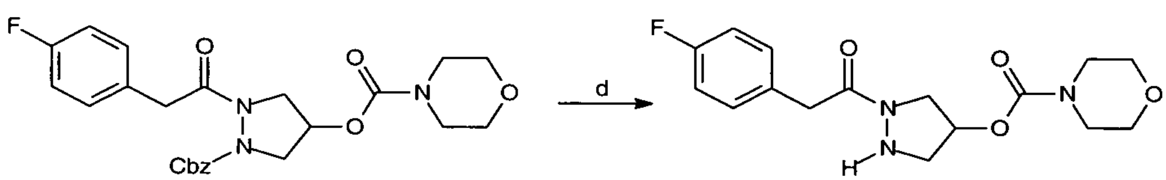
38 **39**

Reagents and conditions: (b) *p*-nitrorphenyl chloroformate, CH_2Cl_2, pyridine, 0 °C 1 hr, rt 12 hr.



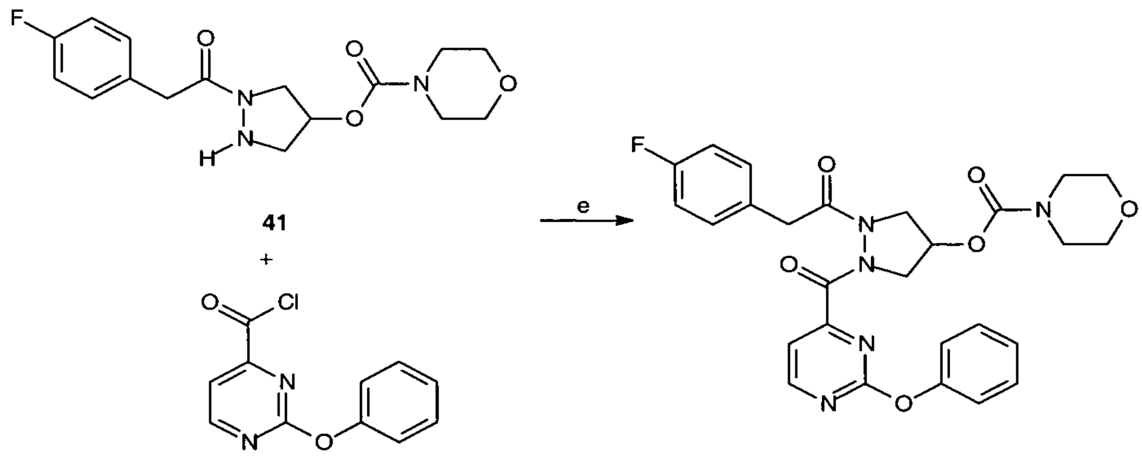
39 **40**

Reagents and conditions: (c) morpholine, CH_2Cl_2, rt 1.5 hr.



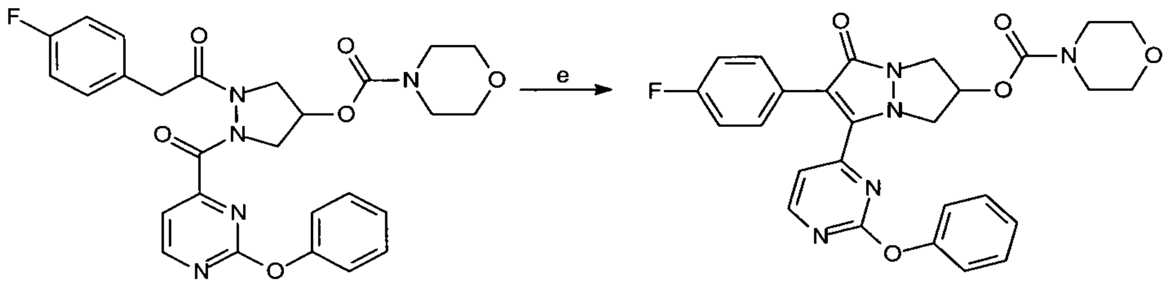
40 **41**

Reagents and conditions: (d) H_2, Pd/C; MeOH:, rt 2.5 hr.



41 + 18 → 42

Reagents and conditions: (e) 1N NaOH, CH_2Cl_2.



42 → 43

Reagents and conditions: (b) NaH. THF, DMF: -10 °C 1 hr, 0 °C 2 hr.

EXAMPLE 12

Morpholine-4-carboxylic acid 6-(4-fluorophenyl)-5-oxo-7-(2-phenoxypyrimidin-4-yl)-2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl ester (43)

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-hydroxy-pyrazolidine-1-carboxylic acid benzyl ester (38): 2-[2-(4-Fluorophenyl)acetyl]-4-oxo-pyrazolidine-1-carboxylic acid benzyl ester, **11**, (1.0 g, 2.81 mmol) is dissolved in THF (30 mL) and the solution cooled to –78 °C. A 5.0 M solution of borane-dimethyl sulfide complex in ether (1.2 mL, 5.61 mmol) is added dropwise. After 1 hour at –78 °C, the reaction is quenched by slow addition of NH_4Cl (sat. aq.) (10 mL). The cooling bath is then removed, and the mixture allowed to warm to room temperature with vigorous stirring. The THF is removed *in vacuo* and the residue diluted with water (50 mL). The mixture is

extracted with ethyl acetate (2 X 100 mL), dried, filtered and concentrated *in vacuo* to give a yellow oil which is purified over silica (1:1 to 1:2 hexane/ethyl acetate to 100% ethyl acetate) to afford 731 mg (73% yield) as a clear, viscous oil.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-(4-nitro-phenoxycarbonyloxy)-pyrazolidine-1-carboxylic acid benzyl ester (39): 2-[2-(4-Fluorophenyl)acetyl]-4-hydroxy-pyrazolidine-1-carboxylic acid benzyl ester, **38**, (366 mg, 1.02 mmol) is dissolved in dichloromethane (10 mL). The solution is cooled to 0 °C and *p*-nitrophenyl chloroformate (411 mg, 2.04 mmol) is added in one portion. The solution is stirred at 0 °C, and pyridine (198 μL, 2.45 mmol) added. Stirring is continued at 0 °C for 1 hour followed by stirring at room temperature for 12 hours. The reaction is diluted with water (40 mL) and extracted with dichloromethane (40 mL). The organic layer is washed with 0.5 N NaOH (2 X 40 mL). The combined aqueous layers are back-extracted extracted with dichloromethane (30 mL). The combined organic layers are washed with brine (30 mL), dried, filtered, and concentrated *in vacuo*. The crude material is purified over silica (3:1 to 2:1 to 1:1 hexane/ethyl acetate) to afford 462 mg (86% yield) of the desired product as a white foam.

Preparation of morpholine-4-carboxylic acid 1-benzyloxycarbonyl-2-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester (40): 2-[2-(4-Fluorophenyl)acetyl]-4-(4-nitro-phenoxycarbonyloxy)-pyrazolidine-1-carboxylic acid benzyl ester, **39**, (462 mg, 0.882 mmol) is dissolved in dichloromethane (9 mL). Morpholine (770 μL, 8.82 mmol) is added and the reaction immediately develops a light yellow color. After stirring about 1.5 hours at room temperature, the reaction is diluted with dichloromethane (20 mL) and washed with a 5% solution of Na_2CO_3 (2 X 20 mL). The combined aqueous layers are extracted with dichloromethane (20 mL), the organic layers combined, washed with water, brine, and dried. The solvent is removed *in vacuo* to afford 414 mg of the desired product as a clear oil.

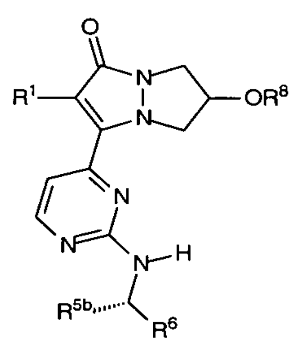
Preparation of morpholine-4-carboxylic acid 1-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester (41): morpholine-4-carboxylic acid 1-benzyloxycarbonyl-2-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester, **40**, (512 mg, 1.09 mmol) is dissolved in methanol (10 mL) and the flask flushed with nitrogen then charged with 10% palladium on carbon (103 mg). The reaction mixture is vigorously stirred and hydrogenated at 1 atmosphere for 2.5 hours at room temperature. The reaction mixture is filtered through a pad of Celite, rinsed with ethyl acetate (100 mL) and concentrated *in vacuo* to afford 354 mg of the desired product as a white powder.

Preparation of morpholine-4-carboxylic acid 1-[2-(4-fluorophenyl)acetyl]-2-(2-phenoxypyrimidine-4-carbonyl)-pyrazolidin-4-yl ester (42): Morpholine-4-carboxylic acid 1-[2-(4-fluorophenyl)acetyl]-pyrazolidin-4-yl ester, **41**, (354 mg, 1.05 mmol) and 2-phenoxypyrimidine-4-

carbonyl chloride, **18**, (345 mg, 1.47 mmol) are dissolved in dichloromethane (2 mL). 1.0 N NaOH (3 mL) is added dropwise at room temperature while vigorously stirring. The reaction is allowed to proceed for 12 hours after which time additional acid chloride, **18**, is added and stirring continued for 3 hours. Additional acid chloride, **18**, (83 mg) is added and stirring continued for an additional 12 hours. After which time the reaction is diluted with dichloromethane (50 mL) and washed with water (50 mL). The combined organic layers are washed with $NaHCO_3$ (sat.) (50 mL) and brine (50 mL), dried, filtered and concentrated to provide a brown oil. The crude material is purified over silica (100% ethyl acetate to 5% methyl alcohol/ethyl acetate) afford 348 mg (61% yield) of the desired product as a viscous oil.

Preparation of morpholine-4-carboxylic acid 6-(4-fluorophenyl)-5-oxo-7-(2-phenoxypyrimidin-4-yl)-2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-2-yl ester (43); A solution of morpholine-4-carboxylic acid 1-[2-(4-fluorophenyl)acetyl]-2-(2-phenoxypyrimidine-4-carbonyl)-pyrazolidin-4-yl ester, **42**, (154 mg, 0.287 mmol) in dimethylformamide (3 mL) is added dropwise to a -10 °C suspension of sodium hydride (16.4 mg of a 60% dispersion in mineral oil, 0.410 mmol) in tetrahydrofuran (3 mL). After 1 hour at -10 °C, the reaction was warmed to 0 °C for 2 hours. The orange-colored solution is then quenched by slowly adding saturated NH_4Cl (400 μL). The cooling bath is removed, and the solution allowed to warm to room temperature. The reaction mixture is concentrated *in vacuo* and the resulting residue is dissolved in THF (25 mL) and filtered through a pad of Celite. The filtrate is concentrated *in vacuo* and the residue purified by Prep HPLC to afford 47 mg (32% yield) of the desired product as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 4.9 Hz, 1H), 7.47–7.18 (m, 9H), 7.08 (t, J = 8.7 Hz, 2H), 6.89 (d, J = 4.9 Hz, 1H), 5.66 (m, 1H), 4.16 (m, 2H), 4.02 (d, J = 12.9 Hz, 1H), 3.87 (dd, J = 12.9, 5.1 Hz, 1H), 3.79–3.30 (m, 8H); HRMS *m/z* calcd for $C_{27}H_{25}FN_5O_5$ (MH^+) 518.1840, found 518.1815.

The third aspect of Category III analogs relates to amino analogs having the formula:



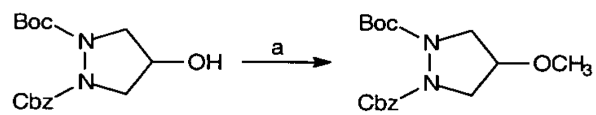
wherein R units are amines having the formula $-NH[CHR^{5b}]R^6$, and R^1, R^{5b}, R^6 and R^8 are described herein below in Table VIII.

TABLE VIII

No.	R^1	R^{5b}	R^6	R^8
311	4-fluorophenyl	H	phenyl	methyl
312	4-fluorophenyl	H	4-fluorophenyl	methyl
313	4-fluorophenyl	H	2-aminophenyl	methyl
314	4-fluorophenyl	H	2-methylphenyl	methyl
315	4-fluorophenyl	H	4-methylphenyl	methyl
316	4-fluorophenyl	H	4-methoxyphenyl	methyl
317	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	methyl
318	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	methyl
319	4-fluorophenyl	H	pyridin-2-yl	methyl
320	4-fluorophenyl	H	pyridin-3-yl	methyl
321	4-fluorophenyl	H	H	methyl
322	4-fluorophenyl	H	methyl	methyl
323	4-fluorophenyl	H	ethyl	methyl
324	4-fluorophenyl	H	vinyl	methyl
325	4-fluorophenyl	H	cyclopropyl	methyl
326	4-fluorophenyl	H	cyclohexyl	methyl
327	4-fluorophenyl	H	methoxymethyl	methyl
328	4-fluorophenyl	H	methoxyethyl	methyl
329	4-fluorophenyl	H	1-hydroxy-1-methylethyl	methyl
330	4-fluorophenyl	H	$-CO_2H$	methyl
331	4-fluorophenyl	methyl	phenyl	methyl
332	4-fluorophenyl	methyl	4-fluorophenyl	methyl
333	4-fluorophenyl	methyl	2-aminophenyl	methyl
334	4-fluorophenyl	methyl	2-methylphenyl	methyl
335	4-fluorophenyl	methyl	4-methylphenyl	methyl
336	4-fluorophenyl	methyl	4-methoxyphenyl	methyl
337	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	methyl
338	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	methyl
339	4-fluorophenyl	methyl	pyridin-2-yl	methyl
340	4-fluorophenyl	methyl	pyridin-3-yl	methyl
341	4-fluorophenyl	methyl	H	methyl
342	4-fluorophenyl	methyl	methyl	methyl
343	4-fluorophenyl	methyl	ethyl	methyl
344	4-fluorophenyl	methyl	vinyl	methyl
345	4-fluorophenyl	methyl	cyclopropyl	methyl

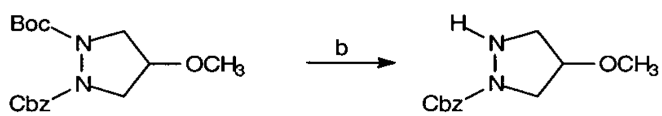
346	4-fluorophenyl	methyl	cyclohexyl	methyl
347	4-fluorophenyl	methyl	methoxymethyl	methyl
348	4-fluorophenyl	methyl	methoxyethyl	methyl
349	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl	methyl
350	4-fluorophenyl	methyl	$-CO_2H$	methyl

The analogs which comprise the third aspect of Category III of the present invention can be prepared using the procedure outlined herein below beginning with intermediate **28**.



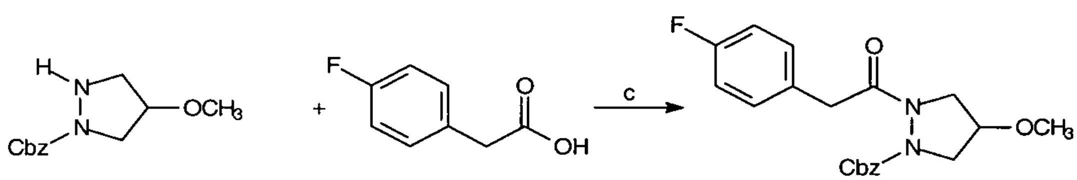
28 **44**

Reagents and conditions: (a) CH_3I, Ag_2O, DMF, dark, rt,12 hr.



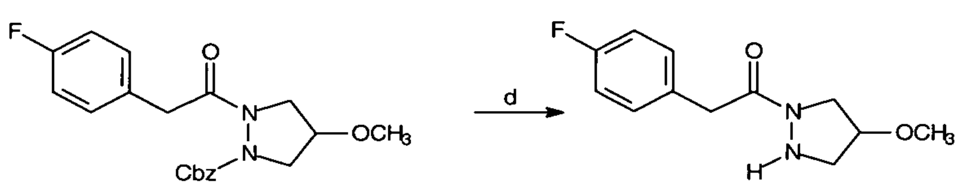
44 **45**

Reagents and conditions: (b) $SOCl_2$, MeOH; 0 °C to rt, 12 hr.



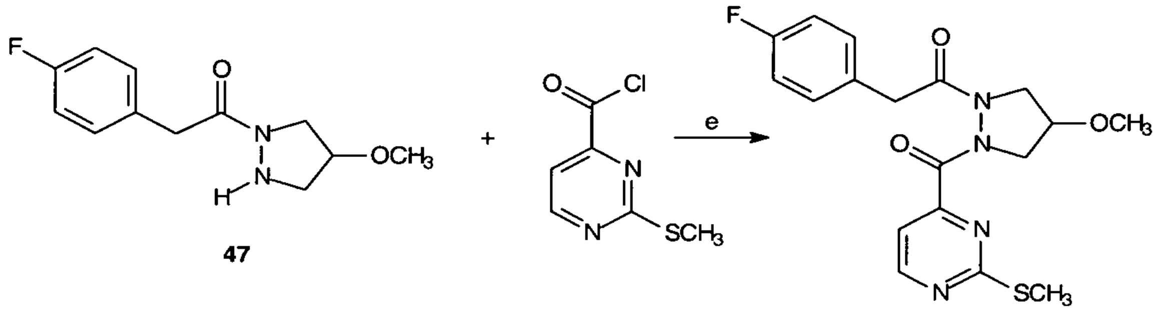
45 **46**

Reagents and conditions: (c) RCOCl, NaOH; rt, 6 hr.



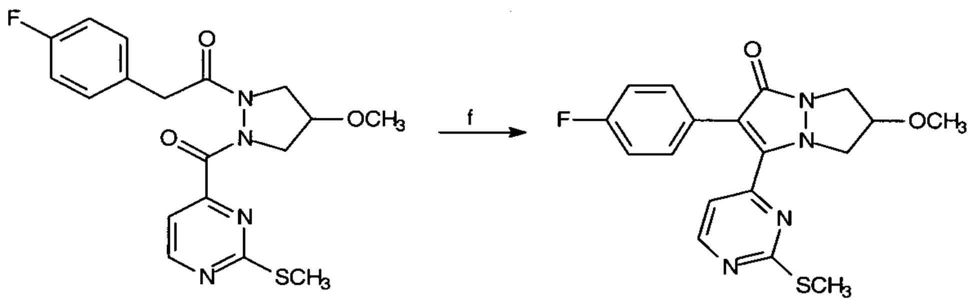
46 **47**

Reagents and conditions: (6) H_2: Pd/C, MeOH; rt,, 3 hr.



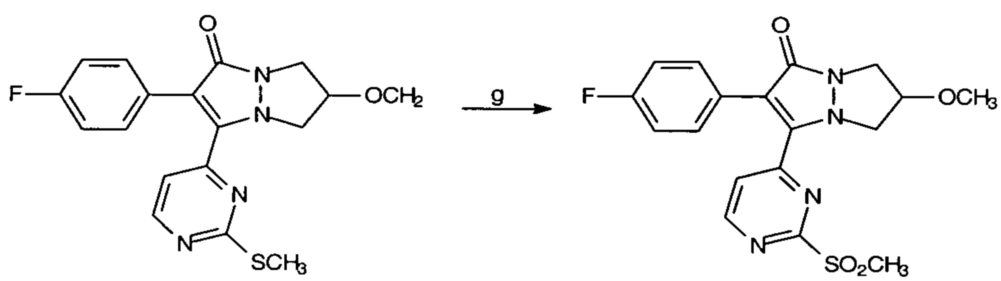
47 48

Reagents and Conditions: (e) NaOH: CH_2Cl_2/water, rt 4 hr.



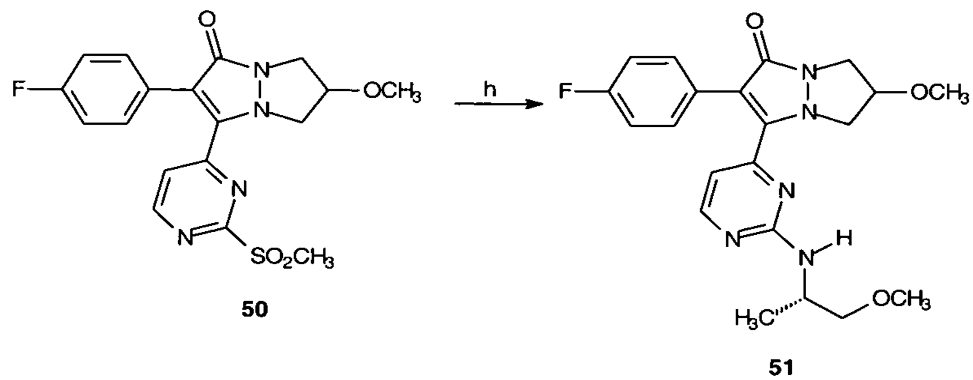
48 49

Reagents and Conditions: (h) NaH, DMF; 0 °C to t, 2 hr.



49 50

Reagents and Conditions: (g) *m*-chloroperbenzoic acid; CH_2Cl_2; rt 30 min.



Reagents and Conditions: (h) toluene: 120 °C 2 hr.

EXAMPLE 13

2-(4-fluorophenyl)-6-methoxy-3-[2-(2-(S)-methoxy-1-methylethylamino)-pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (51)

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-methoxy-pyrazolidine-1-carboxylic acid benzyl ester (44): 2-[2-(4-Fluorophenyl)acetyl]-4-hydroxy-pyrazolidine-1-carboxylic acid benzyl ester, **28**, (2.55 g, 7.91 mmol) is dissolved in dimethylformamide (40 mL). Methyl iodide (1.97 mL, 31.6 mmol) is added followed by silver oxide (3.67 g, 15.8 mmol). The flask is cover with foil and stirred overnight in the absence of light. The reaction mixture is poured into ether (150 mL). The mixture is stirred vigorously at room temperature and filtered through a pad of Celite. The filtrate is washed with water (2 X 150 mL) and brine (150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 2.58 g (97% yield) of the desired product as a yellow, clear oil.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-(4-methoxy)-pyrazolidine-1-carboxylic acid benzyl ester (45): 2-[2-(4-fluorophenyl)acetyl]-4-methoxy-pyrazolidine-1-carboxylic acid benzyl ester, **44**, (2.57 g, 7.64 mmol) is dissolved in methyl alcohol (75 mL) and the solution cooled to 0 °C. Thionyl chloride (5.58 mL, 76.4 mmol) is added dropwise and the reaction is allowed to warm to room temperature overnight. The reaction solution is concentrated *in vacuo* to afford 2.07 g (99% yield) of the desired product as the HCl salt as an off-white solid.

Preparation of 2-[2-(4-fluorophenyl)acetyl]-4-methoxy-pyrazolidine-1-carboxylic acid benzyl ester (46): 2-[2-(4-Fluorophenyl)acetyl]-4-(4-methoxy)-pyrazolidine-1-carboxylic acid benzyl ester, **45**, (8.81 g, 32.3 mmol) is dissolved in dichloromethane (150 mL). 4-fluorophenylacetyl chloride (5.31 g, 38.8 mmol) is added followed by a 0.5 N aqueous solution of sodium hydroxide (150 mL). The mixture is stirred vigorously at room temperature for 6 hours. The reaction is diluted with dichloromethane (200 mL) and washed with water (200 mL). The aqueous layer is extracted with dichloromethane (2 X 200 mL). The combined organic layers are

washed with 5% aqueous sodium carbonate solution (250 mL) and brine (250 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 12.0 g of the desired product as a viscous, tan oil.

Preparation of 2-(4-fluorophenyl)-1-(4-methoxy-pyrazolidin-1-yl)-ethanone (47): 2-[2-(4-Fluorophenyl)acetyl]-4-methoxy-pyrazolidine-1-carboxylic acid benzyl ester, **46**, (12.0g, 32.2 mmol) is dissolved in methyl alcohol (300 mL). The flask is flushed with nitrogen and charged with 10% palladium on carbon (1.2 g). The reaction mixture is stirred vigorously at room temperature under 1 atmosphere of hydrogen gas for 3 hours. The flask is flushed with nitrogen and the reaction mixture filtered through a pad of Celite, rinsing with ethyl acetate (100 mL). The filtrate is concentrated *in vacuo* to afford 7.67 g of the desired product as a viscous, clear oil.

Preparation of 2-(4-fluorophenyl)-1-[4-methoxy-2-(2-methylsulfanyl-pyrimidine-4-carbonyl)pyrazolidine-1-yl]-ethanone (48): 2-(4-Fluorophenyl)-1-(4-methoxy-pyrazolidin-1-yl)-ethanone, **47**, (7.67 g, 32.2 mmol) and 2-methylsulfonyl-pyrimidine-4-carbonyl chloride (9.11 g, 48.3 mmol) are dissolved in dichloromethane (150 mL). A 0.5 N aqueous solution of sodium hydroxide (150 mL) is added steadily *via* addition funnel and the mixture is stirred vigorously at room temperature for 4 hours. The reaction is diluted with 5% aqueous sodium carbonate solution (1 L). The mixture is extracted with dichloromethane (6 X 200 mL). The combined organic layers are dried over magnesium sulfate, filtered and concentrated to give a red oil. The crude material is purified by over silica (1:1 to 1:3 hexane/ethyl acetate to 100% ethyl acetate) to afford 10.3 g of the desired product as a brown, viscous oil.

Preparation of 2-(4-fluorophenyl)-6-methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (49): A solution of 2-(4-fluorophenyl)-1-[4-methoxy-2-(2-methylsulfanyl-pyrimidine-4-carbonyl)pyrazolidine-1-yl]-ethanone, **48,** (2.04 g, 5.22 mmol) in 1:1 dimethylformamide/tetrahydrofuran (30 mL) is added dropwise to a 0 °C suspension of sodium hydride (230 mg of a 60% dispersion in mineral oil, 5.75 mmol) in dimethylformamide (60 mL). After 2 hours at 0 °C, the bright red solution is quenched by slow addition of a saturated aqueous solution of ammonium chloride (5 mL). The cold bath is removed, and the solution allowed to warm to room temperature. The reaction mixture is concentrated *in vacuo* and the resultant residue diluted with ethyl acetate (175 mL). The mixture is washed with a saturated aqueous solution of ammonium chloride (150 mL). The aqueous layer is extracted with ethyl acetate (4 X 75 mL). The combined organic layers are dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material is purified over silica gel (100% ethyl acetate to 5% to 10% to 20% methyl alcohol/ethyl acetate) to afford 1.1 g (57% yield) of the desired product as an orange oil.

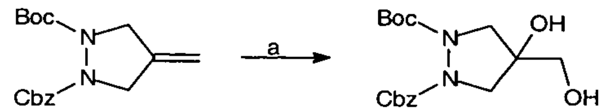
Preparation of 2-(4-fluorophenyl)-6-methoxy-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (50): 2-(4-Fluorophenyl)-6-methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, **49**, (1.10 g, 2.95 mmol) is diluted with dichloromethane (60 mL). 3-Chloroperbenzoic acid (662 mg of ~77% purity, 2.95 mmol) is added all at once to the yellow suspension. After 20 min, additional 3-chloroperbenzoic acid (240 mg, 1.07 mmol) is added. After 10 minutes, the clear, yellow reaction solution is poured in a 10% aqueous solution of sodium bisulfite (60 mL). The layers are separated and the aqueous layer extracted with dichloromethane (2 X 50 mL). The combined organic layers are washed with a saturated aqueous solution of sodium bicarbonate (2 X 50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 948 mg of a mixture of the corresponding sulfoxide and sulfone as a yellow solid. Used as is for next step.

Preparation of 2-(4-fluorophenyl)-6-methoxy-3-[2-(2-(S)-methoxy-1-methylethylamino)-pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (51): 2-(4-Fluorophenyl)-6-methoxy-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one admixture, **50**, (948 mg, 2.44 mmol) and (*S*)-2-amino-1-methoxypropane (652 mg, 7.32 mmol) is diluted with toluene (16 mL). The mixture is heated to 120 °C for 2 hours. The orange solution is allowed to cool to room temperature prior to concentration *in vacuo* to give an orange residue. The crude product is purified over silica (5% to 10% methyl alcohol/dichloromethane) to afford 550 mg of the desired product as a fluorescent yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.1 Hz, 1H), 7.40 (dd, *J* = 8.8, 5.5 Hz, 2 H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 5.1 Hz, 1H), 5.39 (br d, *J* = 8.0 Hz, 1H), 4.57 (m, 1H), 4.30–4.02 (m, 5H), 3.45 (d, *J* = 4.6 Hz, 2H), 3.42 (s, 3H), 3.39 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H); HRMS *m/z* calcd for $C_{21}H_{25}FN_5O_3$ (MH^+) 414.1941, found 414.1945.

Using intermediate **10**, which comprises a 6-methylene unit, the following analog can be prepared using the same procedures as outlined herein above:

2-(4-fluorophenyl)-6-methylene-3-[2-(2-(S)-phenyl-1-methylethylamino)-pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, **52**; ^{1}H NMR ($CDCl_3$, 300 MHz)δ1.60 (d, 3H, *J*= 6.9 Hz), 4.52 (dd, 2H, *J*= 15.9, 24 Hz), 5.08-5.15 (m, 2H), 5.26 (s, 1H), 6.03 (s, 1H), 6.38 (d, 1H, *J*= 5.1 Hz), 7.00-7.05 (m, 2H), 7.22-7.42 (m, 8H), 8.16 (d, 1H, *J*= 5.1 Hz). HRMS: Exact Mass $C_{25}H_{22}FN_5O$ 428.1887 (M^++H), found 428.1871.

Intermediate **10** can also be oxidized under standard conditions, according to the scheme herein below, using OsO_4 to afford the intermediate, **53**:



which can be used to prepare the following:

2-(4-Fluorophenyl)-6-hydroxy-6-hydroxymethyl-3-(2-phenoxypyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, **54**; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.41-3.52 (m, 2H), 3.72-3.86 (m, 3H), 3.94 (d, 1H, *J*= 11.1Hz), 5.23 (t, 1H, *J*= 5.7 Hz), 5.71 (s, 1H), 7.06 (d, 1H, *J*= 4.8 Hz), 7.18-7.34 (m, 5H), 7.40-7.50 (m, 4H), 8.69 (d, 1H, *J*= 4.8 Hz). ESI$^=$ MS: m/z (rel intensity) 435.32 (100, M^++H) Anal. Calculated for $C_{23}H_{19}FN_4O_4$ 0.5H_2O: C, 62.30; H, 4.55; N, 12.63. Found: C, 62.33; H, 4.13; N, 12.41.

Other compounds of the present invention which can be prepared by the procedures or modifications thereof disclosed herein above include the following.

2-(3-trifluoromethylphenyl)-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one;

2-(4-fluorophenyl)-3-(2-(6-aminopyrimidin-4-yloxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one;

2-(4-fluorophenyl)-3-[2-(3-fluorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one;

2-(4-fluorophenyl)-3-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one;

2-(2,4-difluorophenyl)-3-(2-phenoxy-pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one;

2-(4-fluorophenyl)-3-[2-(4-chlorophenoxy)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo-[1,2-a]pyrazol-1-one

2-(4-Fluorophenyl)-3-{2-[1-(*R,S*)-(4-fluorophenyl)ethylamino]pyrimidin-4-yl}-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-{4-[2-(4-Fluorophenyl)-3-oxo-6,7-dihydro-3*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-yl]-pyrimidin-2-ylamino}-propionic acid;

2-{4-[2-(4-Fluorophenyl)-3-oxo-6,7-dihydro-3*H*,5*H*-pyrzolo[1,2-*a*]pyrazol-1-yl]-pyrimidin-2-ylamino}-*N,N*-dimethyl propionamide;

2-(4-Fluorophenyl)-3-(2-([1,3,4]thiadiazol-2-ylamino)pyrimidin-4-yl)-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-{2-[(pyridin-2-ylmethyl)amino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-[(2-methoxypropylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-{2-[(furan-2-ylmethyl)amino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-{2-[(3-benzo[1,3]dioxol-5-yl)amino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-{2-[(1-(propane-1-sulfonyl)piperidin-4-ylamino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

2-(4-Fluorophenyl)-3-{2-(4-methoxybenzylamino)amino]pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one;

The analogs (compounds) of the present invention are arranged in several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

The compounds of the present invention have been found to be surprisingly effective in providing analgesia, or otherwise relieving pain in humans and higher mammals. One convenient means for evaluating pain and for measuring the effective amount of compound(s) necessary to achieve analgesia and, therefore, provide a means for determining the amount of compound(s) which comprises a pharmaceutical composition of the present invention and the amount of compound(s) necessary for use in the methods described herein, is the Rat Thermal Hyperalgesia Model as described herein below.

The Rat Thermal Hyperalgesia Model, i.e., "Hargreaves Method" [Hargreaves, K., et al., *Pain*, (1988), 32:77-88], is used to determine the level at which the systemic administration of test compounds attenuate the hyperalgesia response subsequent to an intraplantar injection of carrageenan. The test results for a non-limiting example of a compound according to the present invention, 2-(4-fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one, (analog 59 from Table I hereinabove) are provided in Table IX herein below.

TABLE IX

Comparison of paw withdrawal latency time following treatment with Analog 59

Treatment	Dose (mg/kg)	Baseline PWL	Post-carrageenan PWL	p-value
Vehicle 0.5%Methycellulose/ 0.5%Tween	5 mL/kg	12.33 ± 0.71	4.64 ± 0.59	na

Compound 59	1	11.82 ± 0.51	9.37 ± 1.24	<0.0001
	5	10.81 ± 0.58	9.45 ± 0.96	<0.0001
	15	11.69 ± 0.76	12.78 ± 0.92	<0.0001

The data in Table IX are expressed as the group mean PWL ± SEM (time in seconds); p-value = one-sided comparison

Analgesia Test Method:

Sprague-Dawley male rats weighing 100-150 g and housed two per shoebox cage in sanitary, ventilated animal rooms with controlled temperature, humidity and regular light cycles are used. Rodent chow and water were allowed *ad libitum*. Animals are acclimated for one week before use. All animal use is in accordance with the United States Department of Agriculture guidelines for humane care.

On the first day of study, each animal is acclimated to test equipment and the baseline paw withdrawal latency (PWL) to a radiant heat source is recorded. The following day, animals are orally dosed with vehicle or test compound. Thirty minutes later, each animal receives a 0.1 mL intra plantar injection of carrageenan (1.2% solution, w/v) into the left hind paw. Four hours post-carrageenan injection, animals are returned to the test equipment to determine PWL of the inflamed paw. The animals are then humanely euthanized with an overdose of carbon dioxide. Statistical analysis of data: Change from pre to post PWL for each animal is calculated. Statistical comparison between treatment groups on these two end points are made via an ANCOVA model with treatment terms, as well as pre-treatment measure as baseline covariate.

The present invention further relates to forms of the present compounds, which under normal human or higher mammalian physiological conditions, release the compounds described herein. One iteration of this aspect includes the pharmaceutically acceptable salts of the analogs described herein. The formulator, for the purposes of compatibility with delivery mode, excipients, and the like, can select one salt form of the present analogs over another since the compounds themselves are the active species which mitigate the disease processes described herein.

Related to this aspect are the various precursor of "pro-drug" forms of the analogs of the present invention. It may be desirable to formulate the compounds of the present invention as a chemical species which itself is not active against the cytokine activity described herein, but instead are forms of the present analogs which when delivered to the body of a human or higher mammal will undergo a chemical reaction catalyzed by the normal function of the body, *inter alia*, enzymes present in the stomach, blood serum, said chemical reaction releasing the parent analog. The term "pro-drug" relates to these species which are converted *in vivo* to the active pharmaceutical.

FORMULATIONS

The present invention also relates to compositions or formulations which comprise the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, the compositions of the present invention comprise:

a) an effective amount of one or more bicyclic pyrazolones and derivatives thereof according to the present invention which are effective for inhibiting release of inflammatory cytokines;

b) an effective amount of one or more compounds having pain relief properties; and

c) one or more pharmaceutically acceptable excipients.

The following are non-limiting examples of compounds having pain relief properties or compounds which are effective in providing relief from pain and which can be suitably combined with the compounds of the present invention:

Acetaminophen, aspirin, difunisal, dipyrone, ibuprofen, naproxen, fenoprofen, fenbufen, ketoprofen, flurbiprofen, indomethacin, ketorolac, diclofenac, floctafenine, piroxicam, celecoxib, and rofecoxib.

The following are non-limiting of adjunct ingredients which may be combined with the compounds of the present invention: Caffeine, compatible amphetamines, compatible antihistamines, compatible antidepressants.

In addition, opioid narcotic analgesics may be combined to form pharmaceutical compositions, for example, oxycodone (Percadan, Percacet, Oxycontin, Tylox), pethidine/meperidine (Demerol), methadone (Physeptone, Dolophine), levorphanol (Dromoran, Levodromoran), hydromorphone (Dilaudid), and buprenorpnine (Temgesic).

The term "effective amount" is defined herein as an amount which achieves the desired pharmaceutical result but which is also within the realm of safe medical practices." For example, it is long been known that the use of some pharmaceutically active compounds, *inter alia*, opiates, can lead to physical or psychological dependency. The amount which comprises the compositions of the present invention can be of varying amounts depending upon the active ingredient, the level of activity of the active ingredient, and the habits and practices as established via testing or those which are long accepted in medical practice.

For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the

compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

The present invention also relates to compositions or formulations which comprise a precursor or "pro-drug" form of the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, these precursor-comprising compositions of the present invention comprise:

a) an effective amount of one or more derivatives of bicyclic pyrazolones according to the present invention which act to release *in vivo* the corresponding analog which is effective in providing analgesia; and
b) one or more pharmaceutically acceptable excipients.

METHOD OF USE

The present invention also relates to a method for controlling the level of one or more inflammation inducing cytokines, *inter alia*, interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) and thereby controlling, mediating, or abating disease states affected by the levels of extracellular inflammatory cytokines. The present method comprises the step of administering to a human or higher mammal an effective amount of a composition comprising one or more of the inflammatory cytokine inhibitors according to the present invention.

Because the inflammatory cytokine inhibitors of the present invention can be delivered in a manner wherein more than one site of control can be achieved, more than one disease state can be modulated at the same time. Non-limiting examples of diseases which are affected by control or inhibition of inflammatory cytokine inhibitors, thereby modulating excessive cytokine activity, include osteoarthritis, rheumatoid arthritis, diabetes, human Immunodeficiency virus (HIV) infection.

It has now been surprisingly discovered that the analogs (compounds) of the present invention are capable of providing analgesia in humans and higher mammals. As such, the present invention relates to a method for providing analgesia and/or pain relief to humans or higher mammals which comprises the step of administering to said human or higher mammal an effective amount of a 6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one described herein above.

The present invention further comprises a method for providing analgesia and/or pain relief to humans or higher mammals which comprises the step of administering to said human or higher mammal a pharmaceutical composition which comprises:

a) an effective amount of one or more bicyclic pyrazolones and derivatives thereof according to the present invention which are effective for inhibiting release of inflammatory cytokines;
b) an effective amount of one or more compounds having pain relief properties; and
c) one or more pharmaceutically acceptable excipients.

The second aspect of the present invention relates to methods for reducing inflammatory bowel syndrome (IBS) in humans and higher mammals, said method comprising the step of administering to a human or high mammal an effective amount of a 6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-one according to the present invention.

Elevated levels of pro-inflammatory cytokines are implicated in many disease states and inhibition of pro-inflammatory cytokine production offers the opportunity to treat or prevent a wide range of diseases and conditions involving elevated levels of pro-inflammatory cytokines. Cytokines have been linked to acute and chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease (IBS), Crohn's disease and ulcerative colitis, for example, see:

i) Rankin, E. C. C., *et al.* **1997**, *British J. Rheum.* 35:334;

ii) Stack, W. A., *et al.* **1997**, *The Lancet* 349:521;

both of which are incorporated herein by reference.

The third aspect of the present invention relates to methods for reducing psoriasis in humans and higher mammals, said method comprising the step of administering to a human or high mammal an effective amount of a 6,7-dihydro-5*H*-pyrazolo[1,2*a*]pyrazol-1-one according to the present invention. It is well established that the control of cytokine activity is directly related to the formation of psoriasis and inhibition of this activity can be used as a therapy to control this condition. For example, see:

Lamotalos J., et al., "Novel Biological Immunotherapies of Psoriasis." *Expert Opinion Invstigative Drugs*; (2003); **12**, 1111-1121.

The present invention, therefore, comprises a method for treating psoriasis in humans which comprises the step of administering to said human a pharmaceutical composition which comprises:

a) an effective amount of one or more bicyclic pyrazolones and derivatives thereof according to the present invention which are effective for inhibiting and/or controlling the release of inflammatory cytokines; and

b) one or more pharmaceutically acceptable excipients.

The above-described composition is also effective as a therapy against the following disease states, and therefore, provides a method for controlling said disease states:

Congestive Heart Failure[1, 2, 3, 4, 5]; hypertension[6]; chronic obstructive pulmonary disease and septic shock syndrome[7]; tuberculosis, adult respiratory distress and asthma[8]; atherosclerosis[9]; muscle degeneration and periodontal disease[10]; cachexia, Reiter's syndrome, gout, acute synovitis, eating disorders, *inter alia*, anorexia and bulimia nervosa[11]; fever, malaise, myalgia and headaches[12]. The following are included herein by reference.

1. Han et al., *Trends in Cardiovascular Medicine*, **10**:19, (2000);
2. Hunter et al., *New Englamnd Journal of Medicine*, **341**:1276, (1999);
3. Behr et al.*Circulation*, **102**:II-289, (2000);

4. Shimamoto et al, *Circulation*: **102**:II-289, (2000);

5. Aukrust et al., *American Journal of Cardiology,*. **83**:376 (1999);

6. Singh, *et al., Journal of Hypertension*, **9**:867 (1996);

7. Dinarello, C. A., *Nutrition* **11**:492 (1995);

8. Renzetti, *et al. Inflammation Res.* **46**:S143;

9. Elhage, *et al., Circulation* **97**:242 (1998);

10. Howells, *Oral Dis.* 1:266 (1995);

11. Holden, *et al., Medical Hypothesis* **47**:423 (1996);

12. Beisel, *American Journal of Clinical Nutrition*, **62**:813 (1995).

PROCEDURES

The compounds of the present invention can be evaluated for efficacy, for example, measurements of cytokine inhibition constants, K_i, and IC_{50} values can be obtained by any method chosen by the formulator.

Non-limiting examples of suitable assays include:

i) UV-visible substrate enzyme assay as described by L. Al Reiter, *Int. J. Peptide Protein Res.*, **43**, 87-96 (1994).

ii) Fluorescent substrate enzyme assay as described by Thornberry et al., *Nature*, **356**, 768-774 (1992).

iii) PBMC Cell assay as described in U.S. 6,204,261 B1 Batchelor et al., issued March 20, 2001.

Each of the above citations is included herein by reference.

In addition, Tumor Necrosis Factor, TNF-α, inhibition can be measured by utilizing lipopolysaccharide (LPS) stimulated human monocytic cells (THP-1) as described in:

i) K. M. Mohler et al., "Protection Against a Lethal Dose of Endotoxin by an Inhibitor of Tumour Necrosis Factor Processing", *Nature*, **370**, pp 218-220 (1994).

ii) U.S. 6,297,381 B1 Cirillo et al., issued October 2, 2001, incorporated by reference and reproduced herein below in relevant portion thereof.

The inhibition of cytokine production can be observed by measuring inhibition of TNF-α in lipopolysaccharide stimulated THP cells. All cells and reagents are diluted in RPMI 1640 with phenol red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/mL each) and fetal bovine serum (FBS 3%) (GIBCO, all conc. Final). Assay is performed under sterile conditions, only test compound preparation is non-sterile. Initial stock solutions are made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells (2×10^6 cells/mL, final conc.; American Type Culture Company, Rockville, Md.) are added to 96 well polypropylene round bottomed culture plates (Costar 3790; sterile) containing 125 μL test compound (2-fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration should not exceed 0.2% final. Cell

mixture is allowed to preincubate for 30 minutes at 37 °C, 5% CO_2 prior to stimulation with lipopolysaccharide (LPS, 1 μg/mL final; Sigma L-2630, from *E. coli* serotype 0111.B4; stored as 1 mg/mL stock in endotoxin screened diluted H_2O vehicle at –80 °C). Blanks (unstimulated) receive H_2O vehicle; final incubation volume is 250 μL. Incubation (4 hours) proceeds as described above. Assay is to be terminated by centrifuging plates 5 minutes at room temperature, 1600 rpm (4033 g); supernatants are then transferred to clean 96 well plates and stored at –80 °C until analyzed for human TNF-α by a commercially available ELISA kit (Biosource #KHC3015, Camarillo, Ca.). The calculated IC_{50} value is the concentration of the test compound that caused a 50% decrease in the maximal TNF-α production.

All documents cited in the Detailed Description of the Invention are, are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.